VOLUME 102 • OCTOBER 1958 • NUMBER 4

INTERNAL MEDICINE

Internal Medicine and the Training of Internists
Paul S. Rhoads

Phenethyl-, Amyl-, and Isoamylbiguanide in the Treatment of Diabetes Mellitus
William D. Odell, Donald C. Tanner, Donald F. Steiner, and Robert H. Williams

Surfeit and Deficit of Sodium
Maurice B. Strauss, Ezra Lamdin, W. Pierce Smith, and Daniel J. Bleifer

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Dyschondroplasia and Hemangiomata (Maffucci's Syndrome). II
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"Infarctoid Cardiopathy" Produced by Hydrocortisone and Monobasic Sodium Phosphate
Hans Selye and Ignacio de Salcedo

Studies on "Prothrombin Derivatives" in Vitamin K Deficiency
Theodore H. Spaet and Mona Kropatkin

Cystic Medionecrosis with Dissecting Aneurysm of Coronary Arteries
Antonio E. Boschetti and Albert Levine

An Experimental and Statistical Method in the Study of New Drugs
Leo J. Cass, and William S. Frederik

Hemophilus Pyarthrosis in an Adult
Robert F. Dyer, Monroe J. Romansky, and J. Robert Holmes

Meprobamate Idiosyncrasy
N. David Charkes

The Medical Management of Peptic Ulcer
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The Use of Serum Protein Electrophoresis in Clinical Medicine
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Evolution of Mitral Valve Surgery
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Some Interrelations Between Sleep and Disease
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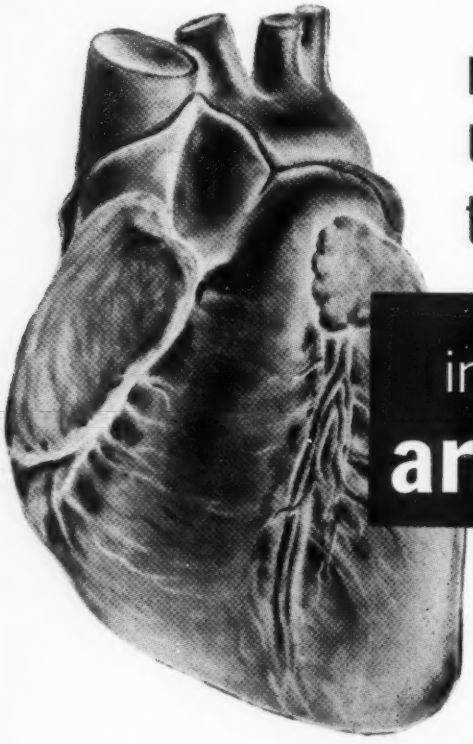

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TABLE OF CONTENTS

VOLUME 102 OCTOBER 1958 NUMBER 4

EDITORIALS

PAGE

Internal Medicine and the Training of Internists
Paul S. Rhoads, M.D., Chicago 515

ORIGINAL ARTICLES

Phenethyl-, Amyl-, and Isoamylbiguanide in the Treatment of Diabetes Mellitus
William D. Odell, M.D.; Donald C. Tanner, M.D.; Donald F. Steiner, M.D., and Robert H. Williams, M.D., Seattle 520

Surfeit and Deficit of Sodium
Maurice B. Strauss, M.D.; Ezra Lamdin, M.D.; W. Pierce Smith, M.D., and Daniel J. Bleifer, M.D., Boston 527

The Epidemiology of Psittacosis and Report of a Turkey-Borne Outbreak
Robert D. Leachman, M.D., and Ellard M. Yow, M.D., Houston, Texas 537

Dyschondroplasia and Hemangiomata (Maffucci's Syndrome). II
William Bennett Bean, M.D., Iowa City 544

"Infarctoid Cardiopathy" Produced by Hydrocortisone and Monobasic Sodium Phosphate
Hans Selye, M.D., and Ignacio de Salcedo, M.D., Montreal 551

Studies on "Prothrombin Derivatives" in Vitamin K Deficiency
Theodore H. Spaet, M.D., and Mona Kropatkin, B.S., New York 558

Cystic Medionecrosis with Dissecting Aneurysm of Coronary Arteries
Antonio E. Boschetti, M.D., and Albert Levine, M.D., Boston 562

An Experimental and Statistical Method in the Study of New Drugs
Leo J. Cass, M.D., Cambridge, Mass., and William S. Frederik, Ph.D., M.D., Wellesley Hills, Mass. 571

Hemophilus Pyarthrosis in an Adult
Robert F. Dyer, M.D.; Monroe J. Romansky, M.D., and J. Robert Holmes, M.D., Washington, D. C. 580

Meprobamate Idiosyncrasy
Capt. N. David Charkes (MC), U. S. Army (Res.) 584

TREATMENT IN INTERNAL MEDICINE

The Medical Management of Peptic Ulcer
Carl G. Morlock, M.D., Rochester, Minn. 594

Evaluation of the Surgical Treatment of Intractable Duodenal Ulcer
Robert M. Zollinger, M.D., Columbus, Ohio 607

REVIEWS OF INTERNAL MEDICINE

The Use of Serum Protein Electrophoresis in Clinical Medicine
Robert L. Wall, M.D., Columbus, Ohio 618

EVOLUTION OF MODERN MEDICINE

Evolution of Mitral Valve Surgery
Donald M. Hayes, M.D., Winston-Salem, N. C. 659

CONTRIBUTIONS OF BASIC SCIENCE TO MODERN MEDICINE

Some Interrelations Between Sleep and Disease
Eugene D. Robin, M.D., Boston 669

BOOKS

Reviews by Dr. William B. Bean and Others 676

REGULAR DEPARTMENTS

News and Comment 684

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VOLUME 102 OCTOBER 1958 NUMBER 4

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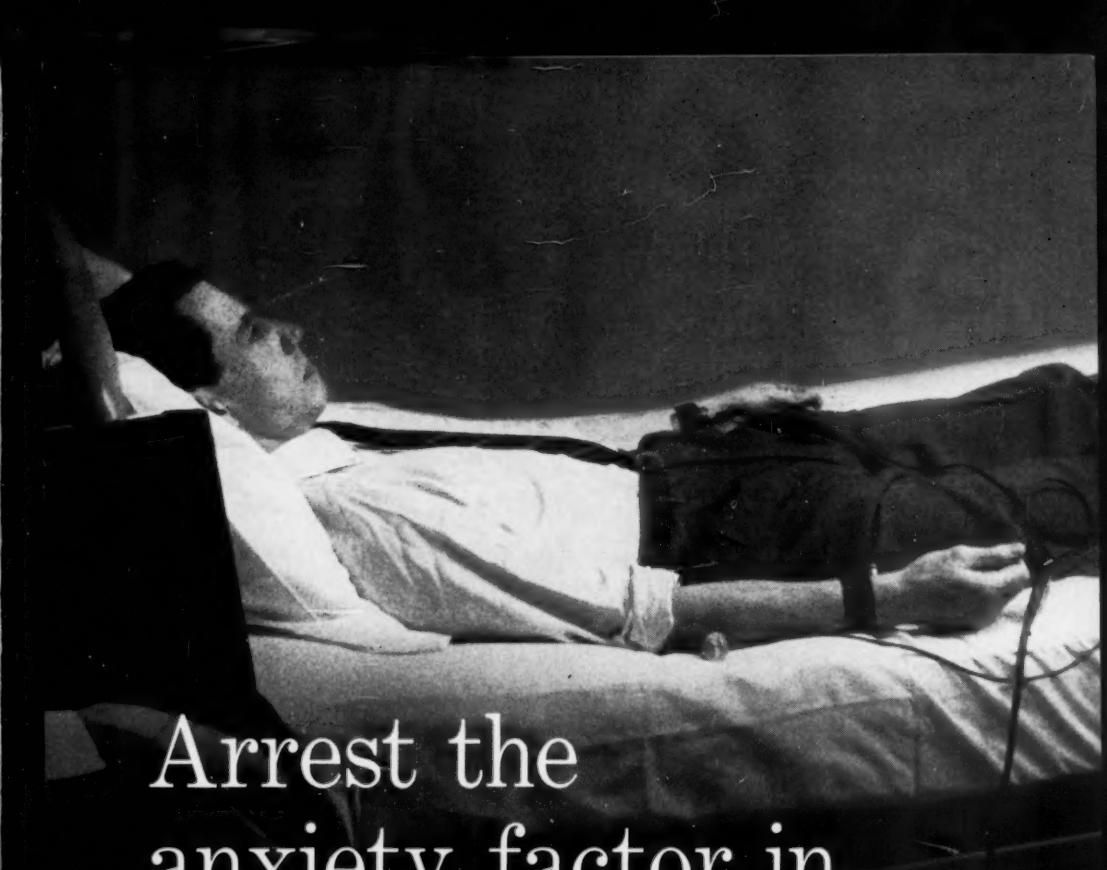

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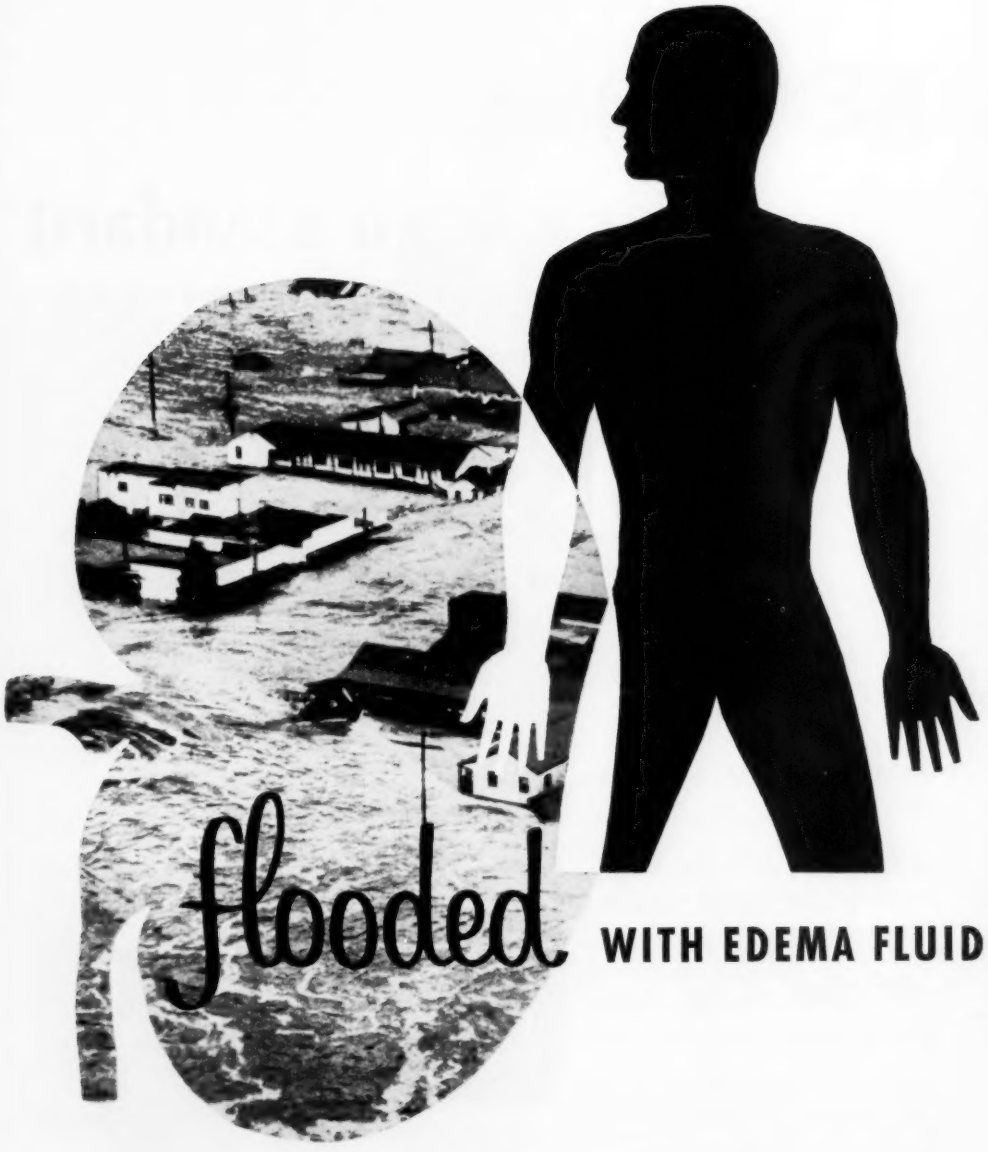

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Editorial

Internal Medicine and the Training of Internists

Most of the readers of this journal, in rare moments of reflection and self-examination, must have pondered the questions: Of what does the practice of internal medicine consist? What is an internist? Since internists are supposed eventually to be certified by a specialty board, the implication is that they practice a specialized type of medicine. Doubtless, in some suitably remote repository the definition of this specialty lies entombed, but the fact remains that among both the public and physicians themselves there is much confusion as to what is embraced by this most all-inclusive of the specialties.

Some dictionaries sensibly ignore the question. A recent edition of Webster's unabridged dictionary defines internal medicine as, "That branch of medicine dealing with the diagnosis and treatment of diseases of the interior of the body," thus separating its practitioners from, at least, their dermatologic colleagues. "Dorland's Illustrated Medical Dictionary" takes a further step in describing it as "that department of medicine which deals with diseases that cannot be treated surgically," a novel segment of human ills delimited only by the imagination and industry of the surgeons. The same source goes a step further by defining an internist as "A physician who treats diseases of the internal organs," thus slicing off another segment. In Funk and Wagnalls large dictionary the only reference to internal medicine points out that this is a "remedy to be taken internally."

Such definitions obviously will not do. Yet, after several frustrating hours of search in one of America's best-equipped medical libraries, I was able to dig out no good statement of what is encompassed by the term. O. H. P. Pepper,[1] after a long preamble in which the difficulties of such an attempt were set forth, had a try at defining the practitioner of the specialty. "An internist is a physician fitted by sound and applicable knowledge of the basic sciences, a continuing training in internal medicine, a familiarity of fields outside his own, and an intellectual rather than a manual or technical approach, to study and treat the diseases of the field of internal medicine to which he strictly limits himself and to integrate with the knowledge of his own field that of the allied specialities." Dr. Pepper then modestly and truthfully admits that, since "internal medicine" eludes definition, this delineation of the internist is perhaps wide of the mark.

When asked to describe the tasks properly to be undertaken by an internist, I could not compose a definition but had this to say [2]:

The average patient probably considers the internist a general practitioner particularly interested in diagnosis who has removed from his armamentarium the scalpel, trephine, forceps, plaster

Submitted for publication July 21, 1958.

cast, and the countless other tools of his craft, confining his own therapeutic efforts to what can be written upon a prescription blank plus the hypodermic needle. This concept may be surprisingly close to the correct one. No specialist can approach in utility to the patient the general practitioner who by incessant study and necessity has mastered the staggering body of medical knowledge and the skills of a dozen surgical specialties required to make him competent to take care of nearly all the needs of those who come to him for help. However, this breed of doctor is almost extinct, for medical knowledge is too diverse and too technical for any one man to acquire all of its essentials.

The "medical man" must strive to come nearest this ideal doctor more than any other of the specialists. It is he to whom the patient may properly turn as having the final word in determining what is the matter and what is to be done. The internist should not operate if a competent surgical colleague is available and usually could not anyway; but he must have enough knowledge of the problems of general surgery, gynecology, obstetrics, otolaryngology, ophthalmology, neurosurgery, genitourinary surgery, and all the other subspecialties so that he will know when surgery is indicated and whom he should call upon for help. Having called in another consultant and concurred in the diagnosis he must accept responsibility for the outcome along with his colleague.

In his delightful essay, "Internal Medicine as a Vocation,"[3] Sir William Osler, while regarding internal medicine as a field set apart, wisely refrains from defining it as a specialty. He says in part:

I wish there were another term to designate the wide field of medical practice which remains after the separation of surgery, midwifery and gynecology. Not itself a specialty (though it embraces, at least, half a dozen) its cultivators cannot be called specialists, but bear without reproach the good old name physician, in contradistinction to general practitioners, surgeons, obstetricians and gynecologists.

He then goes on to point out his own high standards for those to be regarded as internists. Among his recommendations were a 10-year period of "dry bread years" in which were recommended study abroad or at least in other medical centers in this country, some years in general practice, much work with outpatients and without too much preoccupation with "quiz classes" and "journal work." He strongly advised more than passing familiarity with one or all of the disciplines of chemistry, physiology, and morbid anatomy. Of the three, some special knowledge of morbid anatomy was considered most essential for the clinician.

It is obvious that the composite of "internal medicine" cannot be neatly encompassed by a definition. There are just as obviously widely differing opinions as to the kind and amount of training required by those who wish to be internists. To some this dilemma may appear to be of purely academic importance. To others, who after five years of postgraduate preparation are about to take Board of Internal Medicine examinations, the question is practical and urgent. Upon their estimate of what, in the minds of the Board examiners, makes up the body of facts and skills which the internist should have for minimum equipment can depend success or failure in the Board examinations. Without going into the question of whether one who fails in the examination can or cannot be as effective an internist as one who passes, the fact is that unsuccessful candidates for Board certification are for the most part denied recognition as capable consultants. Admission to many hospital staffs and medical societies, advancement in academic rank in medical schools, and other privileges are denied to them. Members of the Board have from time to time deplored this practice of making differentials in emoluments and promotions contingent on Board certification, but the practice is here, and young internists know they had better get Board certification. One of the kindest and wisest of the Board chairmen gave the admonition that "the responsibility of acquiring knowledge rests with the candidate and the respon-

sibility of maintaining the standards of knowledge required for certification rests with the Board." [4] In the long run, however, the future of internal medicine depends largely not upon what each person thinks should make him a good internist but what the Board collectively thinks.

Up to now, there has been little to criticize in either the personnel or the decisions of the Board of Internal Medicine. From the outset, thoughtful conscientious men have tried to lay down rules rigid enough to assure quality in the product of the training programs but flexible enough not to cramp the individual interests of the candidates in these all-important years of their development.

In 1940 Dr. Irons [5] quoted from the brochure of the Board:

The American Board of Internal Medicine does not propose to establish fixed rules for the preliminary training of candidates for certification in this field. Broad general principles for training, however, may be outlined—"A sound knowledge of physiology, biochemistry, pharmacology, anatomy, bacteriology and pathology as they apply to disease is essential for continued professional growth of the individual who practices internal medicine. Such knowledge may be acquired in a number of ways. These include sciences closely integrated with clinical facilities, and service in well organized clinics or in preceptorships."

No one can question the desirability of such emphasis on the nonclinical disciplines or the wisdom of the declaration to keep the program very flexible, and yet time spent in a preceptorship part of the original program [6] is now unacceptable to the Board and for very understandable reasons.

There are differences of opinion as to what constitutes "sound knowledge" of the nonclinical subjects listed above. Some members question whether one year in one or more of these branches is enough—certainly there can be no prolonged special training in *all* of them. Others question the value of even a year of research experience as an integral part of the training of a resident. Lewis [7] feels that above all else an internist must have the capacity to make a thorough physical examination and to take a good history and make a penetrating analysis of it. In his view two years is too little time to develop in most of the candidates the broad knowledge of medicine and clinical skills that are required of internists. He thinks only those with more than average interest and aptitude for research should be required to participate in it. "If we are to do our job as I see we should do it, we will have to take an almost heretical course and decide that we will train some of our apt young men to become expert clinicians and clinical teachers and others to be investigators."

These points are well taken. The Board has made a real effort to make the program for qualification flexible enough to adapt itself to the special circumstances of physicians who have prepared themselves as specialists in internal medicine in a variety of ways. Plan H, the one most recently adopted, makes it possible for a man committed particularly to research and academic medicine to spend the two required postresidency years chiefly in the laboratory, provided he keeps his hand in clinical medicine by work in the hospital wards or dispensary once a week. Such men must be specially recommended for this privilege by the professors of medicine in the schools which they serve.

Whether other young internists not aiming for teaching careers but with strong research interests could not similarly benefit from two years with more emphasis on research and less on "practice" is a question that must be answered on an individual basis.

Dr. Irons, in his discussion of Board examinations points out that the written questions are so designed as to test the powers of the candidates to come to proper

conclusions after certain clinical data are stated rather than to delve too deeply into their factual knowledge. In grading, more attention is given to logical deductions than to "right answers." Such emphases in evaluating the examinees are praiseworthy but difficult of attainment. Even more difficult, but much more important at this stage of a young man's development, is the evaluation of intangibles. In other words, what kind of a doctor should be encouraged to enter the field of internal medicine?

1. Is he impulsive or does he have the patience for long hours of continued study and for careful but monotonous tasks in the laboratory?

2. Does he have the conviction that *every* patient is important and worthy of his help whether he can pay for it or not?

3. Does he have sustained enthusiasm? Will he willingly undertake the painstaking preparation required to make him a good teacher?

4. Does he have enough devotion to his job to look up what he doesn't know, to make house calls, to get up at night when needed?

5. When called upon for a consultation will his efforts be devoted to helping his colleague to do what is best for the patient or to impressing the patient?

No one will deny the importance of such intangibles, yet how can an examining Board make such evaluation?

No Board can make rules which will answer all of these special problems of the peculiar division of medicine occupied by the internists, and yet a recognition of the problems suggests some changes that might help.

The present steps being taken by investigating committees from the College of Physicians to learn more about what makes up the residency program in the various approved hospitals should prove most constructive. If carried on perceptively it could furnish some indication of what the various internists in charge of residency programs consider important and of the way these ideas are implemented. More important, some evaluation of the teachers themselves could be had.

From an interchange between teachers in the various hospitals and the Board more minds could be brought to focus on the problem of arriving at some clearer definition of the minimum body of knowledge and skills which should reasonably be required of all internists. Perhaps an examination devised to test a candidate's grasp of the "fundamentals" so agreed upon could be given at the *end of the three-year residency program.* Successful candidates could then go about the next stage of their "dry bread" period pursuing their particular fields of interest in a more relaxed frame of mind.

Only those who have seen young men "sweat out" the year or two before their examination frantically reading textbooks and journals in the hope of cramming in enough facts in all the fields of internal medicine to satisfy the examiners can be aware of the anxiety produced in them. Few persons will question the value of high standards and the necessity of examinations to maintain them. However, could not these two or three years be spent more usefully if a candidate could be assured that the decision regarding his certification would be made on the basis of such points as the following?

1. Consideration of a comprehensive report on his performance by certified internists and faculty members of medical schools to whom the candidates had been assigned for guidance and supervision. From these reports would come information on the "intangibles."

2. Demonstration of the ability to take a good history, make a good physical examination, and make logical conclusions and recommendations after reviewing the laboratory data on one or two patients chosen at random.

3. Demonstration of a fairly good grasp of fundamental knowledge of internal medicine as a whole plus more complete knowledge in the field of his special interest, such as cardiology, metabolic diseases, or infectious diseases.

Implementing of Point 3 would require assignment of candidates to examiners, some of whom would have special interests in the same field as those of the candidate. In case of disagreement in evaluation by two examiners, a third should be called in before a candidate is failed. At this stage of a man's training the psychologic impact of failing is too devastating for the decision to be reached with any hint of haste or unfairness. If an unfavorable verdict is reached, and inevitably this will happen in many cases, the candidate should be entitled to a consultation with members of the examining board for counsel as to how his deficiencies might best be remedied or whether or not he should change direction.

It should be pointed out again that I have the highest admiration for every one of the present members of the Board of Internal Medicine and a profound appreciation of the difficult task they face.

In friendly discussions various members sharply disagree with some points brought up here—on perfectly reasonable grounds. However, since our specialty has special problems not faced by more narrow ones, a full discussion of the manner in which its practitioners are to be trained seems to be in order. The public should be assured of a quality product. On the other hand, care must be taken not to cramp the development of young men of imagination and unusual initiative by insisting on a too rigidly standardized training program.

PAUL S. RHOADS, M.D.,

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Phenethyl-, Amyl-, and Isoamylbiguanide in the Treatment of Diabetes Mellitus

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In 1926, Frank et al.[1] synthesized Synthalin A (decamethylenediguanidine) and showed that oral administration of the drug lowered the blood sugar remarkably in partially depancreatized animals and in human diabetics. A few diabetic patients were treated with Snythalin A, but it was subsequently proved to be quite toxic even in small doses,[2,3] producing histological changes in the liver and kidney after one or two days, and all clinical use of the drug was discontinued. However, other compounds containing this guanidine group (Fig. 1) were not so toxic. Indeed, it is known that normal body constituents such as creatine and arginine contain the guanidine group. Also, Paludrine [N_1-(*p*-chlorophenyl)-N_5-isopropylbiguanide] has a mild hypoglycemic action, and it has been used successfully for several years in the treatment of malaria.[12,13]

Recently, in a search for hypoglycemic compounds, Ungar[4] found that phenethylformamidinyliminourea (also referred to as phenethyldiguanide, or DBI, but preferably called phenethylbiguanide, or PEBG) was an effective oral agent for lowering blood sugar. The action of this compound has been studied by Ungar, Williams, Tyberghein, Nielsen, Krall, Steiner, and their co-

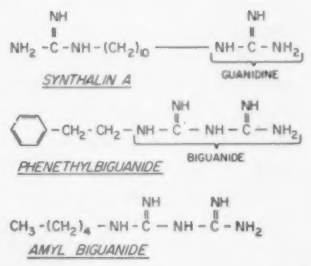

Fig. 1.—Formulae of biguanide compounds.

workers.[4-9] They found that the drug did not produce any histological lesions in guinea pigs and rats. In human subjects, the only reported untoward reactions have consisted chiefly of anorexia, nausea, and vomiting.

The hypoglycemic effect of the drug results from a decreased glucose output by the liver and increased glucose uptake by muscles. From one point of view these actions seem ideal, since in diabetes there is an overproduction and underutilization of glucose. However, in contrast to insulin, PEBG decreases muscle glycogen deposition and oxygen uptake and causes a greater increase in lactic acid production. It is therefore concluded that PEBG increases anaerobic glycolysis. These alterations have been attributed to an inhibitory effect of the biguanides on certain respiratory and oxidative enzymes, predominantly cytochrome oxidase.[9]

Some of the major actions of PEBG are like those of Snythalin A, but experiences thus far have indicated a marked difference between these two compounds with respect to toxicity.

Using these studies as a foundation, we have treated 61 diabetic patients with one

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Dr. Emily Fergus cooperated in and referred patients for use in this study.

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or more of three biguanide compounds: phenethyl-, amyl-, and isoamylbiguanide (Fig. 1), hereafter referred to as PEBG, ABG, and IABG, respectively. All of these drugs were administered orally in tablet form. This report is based upon our preliminary clinical experience with these compounds.

Methods

The only diabetic patients who were not treated with biguanides were those with renal or liver disease. (Eleven of these patients also had tuberculosis and were on isoniazid and PAS. This had no apparent effect on the mechanisms or results of biguanide therapy.) Immediately before starting on one of these drugs, each patient had a complete physical examination, urinalysis, hematocrit, white blood cell count, sulfobromophthalein (Bromsulphalein) excretion test, cephalin flocculation test, and blood urea nitrogen determination. Whenever possible, measurements of fasting blood sugars were made when the patients were not under insulin treatment. All insulin was discontinued in older mild diabetics before treatment with a biguanide was started. Juvenile or severe adult diabetics who were likely to develop acidosis had their insulin doses lowered by 10% to 30% before biguanide therapy was begun. Insulin dosage was then gradually decreased further, in accordance with urine sugar levels and fasting blood sugar values. Blood sugar determinations were carried out by the method of Nelson and Somogyi; urine sugars were measured with Clinitest tablets. After patients had been on biguanide therapy for a period of one to three months, the sulfobromophthalein excretion, cephalin flocculation, blood urea nitrogen, white blood cell count, and hematocrit tests were repeated.

The responses to therapy were rated as follows: (*a*) *good response*—if fasting blood sugars were lowered by 30% or more, with at least a 50% decrease in glycosuria, or if insulin requirements were lowered by 30% or more; (*b*) *little or no response*—less than (*a*), or no response at all.

Results

These 61 patients ranged in age from 14 to 84. There were five whose diabetes had been noted before the age of 20, one acromegalic patient with diabetes, and 55 patients in whom onset of diabetes occurred after the 20th year of life. Thirty-two patients (52%) had a good response according to the criteria mentioned above.

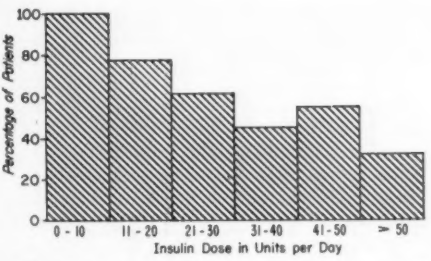

Fig. 2.—Per cent of patients having a "good" response to biguanide therapy plotted against the insulin dose needed to control the diabetes.

Twenty-six patients could be controlled on a biguanide compound alone. Six of these patients had not been well controlled on tolbutamide. Twenty-nine patients (48%) had little or no response. There was no correlation between the age of the patient or duration of diabetes and/or insulin therapy and the response to biguanide therapy. However, there was an inverse relationship between the dose of insulin necessary to control the diabetes and the response to the biguanides (Fig. 2).

Side-effects were of two types: 1. Early side-effects, which generally developed within the first week of therapy, were seen in 60% of the patients treated. These consisted chiefly of anorexia and nausea, which generally progressed to vomiting if therapy was maintained at the same dosage. Two patients experienced diarrhea. These side-effects occurred less frequently if the drugs were administered after meals and could be relieved in some patients when aluminum hydroxide was given with the biguanide. In all cases, either a lower dose of the drug or discontinuation of this therapy resulted in partial clearance of these unpleasant reactions within 4 to 24 hours, and complete clearance was evident after 48 hours. These side-effects seemed to subside somewhat faster after ABG therapy than they did after PEBG or IABG treatment and tended to be less severe. The dose of the particular drug causing side-effects was variable, some patients taking with impunity a dose on which others noted untoward effects. However, as the dose of biguanides was in-

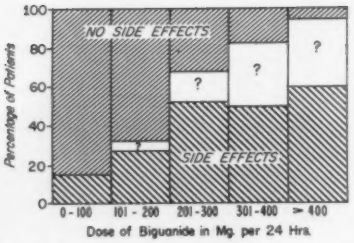

Fig. 3.—Per cent of patients treated with biguanides having side-effects plotted dose (irrespective of particular compound used) of biguanides. Patients having no side-effects on one dose and whose diabetes was controlled on that dose were not placed on higher doses. Thus we do not know at what dose level they would have side-effects. These groups form the areas with the question marks.

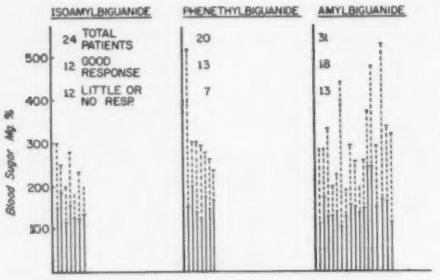

Fig. 4.—Blood sugar levels of patients responding to biguanide therapy (method of Somogyi and Nelson). Final blood sugars in most instances represent the average of two to five determinations. This does not include those patients in whom the insulin dose was gradually lowered because their nontreatment blood sugar level is not known.

creased, the per cent of patients treated having side-effects also increased (Fig. 3). 2. Twenty-eight patients were treated with biguanides for one month or more. Of these, 10 (36%) noted side-effects after they had been on 4 to 16 weeks of apparently successful therapy. Seven of these patients had had mild early side-effects previously, and thus the total incidence of unpleasant reactions to biguanide therapy, both early and late, is 64%. These late side-effects consisted of a 5 to 15 lb. weight loss, weakness, lethargy, and malaise. As far as could be determined by history and examination, the weight loss was not always caused by anorexia, change in diet, or glycosuria. In all cases these effects disappeared promptly when the drug was stopped or if the dose was lowered and insulin therapy was used along with the biguanide. Within a week there was usually a 5 lb. or more gain in weight in these patients. No signs of hepatic or renal damage were found on repeated physical examination, urinalysis, hematocrit, white blood cell count, sulfobromophthalein excretion, blood urea nitrogen test, or cephalin flocculation.

The results of therapy with each of the three drugs are shown in Figure 4 and discussed below. The differences in the percentages of patients responding and side-effects seen under each drug are explained by the fact that some patients were treated with more than one drug.

IABG.—Twenty-four patients were treated with isoamylbiguanide. Doses ranged from 12.5 mg. four times a day to as high as 225 mg. four times a day. Twelve patients (50%) had a good response, and 12 noted little or no response. Side-effects were noted in 11 (46%) patients. One patient had no response to 100 mg. four times a day and no side-effects but was not placed on a higher dose. Nineteen patients had been taking insulin prior to treatment with the biguanides, and their average dose was 29 units a day. (This excludes the acromegalic patient who had marked insulin resistance.)

PEBG.—Twenty patients were treated, and thirteen, or 65%, had a good response. Seven (45%) had little or no response. Side-effects were seen in 12 patients (60%), but these prevented treatment in only 7 patients (45%). Dosages ranged from 25 mg. three times a day to 100 mg. four times a day. Seventeen patients had previously taken insulin, and their average dose was again 29 units a day.

ABG.—Thirty-one patients were treated, with eighteen (or 58%) having a good response. Thirteen (42%) had little or no response. Side-effects were seen in 24 (77%) of patients but were often very mild, usually consisting only of anorexia

and disappearing after lowering the dose of ABG. In 13 patients, these effects prevented continued use of the drug. Dosages ranged from 50 mg. twice a day to 150 mg. four times a day. The average insulin dose was 35 units (again excluding the acromegalic patient).

Several case histories are given to exemplify various responses to biguanide therapy.

Report of Cases

CASE 1 (Labile Juvenile Diabetes).—A white married man, aged 38, had previously been employed full time as an electrician and had had a particularly labile diabetes since the age of 20. He suffered from repeated hypoglycemic attacks and could not be satisfactorily regulated on isophane (NPH) and/or regular insulin and dietary restriction. At one time he had taken four injections of regular insulin and six meals a day without satisfactory control. However, he began to experience convulsions, which eventually occurred at approximately weekly intervals in spite of poor diabetic control and considerable glycosuria. Determinations of the blood sugar at the time of these attacks always demonstrated very low values. When the patient was first seen there was so much mental deterioration that he was no longer employable and he could not care for his diabetes. Institutional care seemed to be indicated. He was taking a total of 45 units of regular insulin per day in four separate doses when he was first placed on ABG therapy. Regulation was ultimately accomplished with 100 mg. four times a day and a single injection of 20 units of isophane insulin. His urine became free of sugar within one week and remained so for four months. During this period he had no further hypoglycemic reactions or convulsions. His personality and mental capacity improved dramatically, and he now cares completely for his diabetes.

After four months of apparently successful treatment, he failed to eat his full evening meal on one occasion and had a generalized seizure about 2 a. m. This was followed in rapid succession by three more in the next six hours. The 10 p. m. dose of ABG was decreased to 50 mg., and he again did well for two weeks. At this time he took 100 mg. of ABG at 10 p. m. because he noted some acetonuria, and again, at about 2 a. m., he had a generalized seizure. He was hospitalized and given dextrose and the morning dose of ABG was omitted. He ate his usual food intake, and two hours after the noon meal and 100 mg. of ABG he had two further seizures.

Further regulation is now in progress, and at present the treatment includes 75 mg. of ABG after breakfast, lunch, and dinner, and 23 units of isophane insulin once daily.

CASE 2 (Adult-Onset Diabetes).—A white woman, aged 71, had long been crippled with contractures secondary to rheumatoid arthritis and had to use a crutch when walking. She entered King County Hospital for the first time on July 19, 1957, with a two-week history of marked polydipsia and polyuria. The blood sugar was 360 mg. %, and the urine yielded 4+ sugar and 4+ acetone reactions. The blood sugar was brought down to normal by 100 units of regular insulin and was maintained with 20 to 40 units daily. Insulin therapy was stopped because the arthritic contractures precluded the patient's giving herself injections, and she was given ABG, 50 mg., three times a day. Her urine continued to show a 4+ sugar reaction, and her blood sugar rose to 338 mg. %. ABG was increased to 75 mg. four times a day, and the glycosuria decreased, but she developed marked anorexia with nausea and vomiting. The dose was changed to 50 mg. four times a day, and within 24 hours she felt well. Her urine became free of sugar on all tests, and she was discharged from the hospital. She remained on this dose for one month, and urine tests, performed four times a day, showed no sugar. The blood sugar values were repeatedly found below 130 mg. %. On Sept. 14, 1957, ABG was stopped, and on Sept. 16, all urine tests showed 4+ sugar reactions. Before the planned blood sugar evaluation could be obtained, the patient started therapy with ABG again, and on Sept. 18, all urine tests were negative. Her dose was lowered to 50 mg. three times a day, and she has remained well controlled to date. Interestingly, she has noted marked relief of arthritic pain and is now active and walking without help.

CASE 3 (Stable Juvenile Diabetes).—A Negro woman, aged 18 had had diabetes for one year and was well controlled on 30 units of isophane and a 2050 Cal. diet. She was treated with ABG, 50 mg. four times a day. Insulin was reduced to 15 units and then stopped completely one week later. She felt well, and her urine remained negative for sugar during the next 14 weeks, and repeated fasting blood sugar tests were below 100 mg. %.

After this period of apparently good diabetic control she developed a mild cough, fever, malaise, headache, and lethargy. This was thought to represent a mild upper respiratory infection, and in about 48 hours the fever and cough subsided, but malaise, headache, lethargy continued and mild diarrhea developed. The diabetes remained in good control, but all these symptoms continued. In 17 days her weight had dropped from 115 to 105 lb., and ABG was discontinued. Twenty-four hours later, she felt greatly improved; her appetite had returned,

the diarrhea had ceased. Insulin was reinstituted, and she regained her weight. She remained well controlled on about 30 units of isophane insulin daily.

Case 4 (Acromegaly with Insulin-Resistant Diabetes).—A 38-year-old white man had had classical acromegaly for 10 years. Diabetes had developed when the patient was 34 and had been initially controlled on 70-80 units of isophane insulin. Subsequently he developed an urticarial rash and lente insulin was then used instead. Eventually, 110 units per day was required for proper regulation. In the next year, the insulin requirement increased until he was taking 600 units per day.

When first seen, he was on 160 units of lente insulin and spilling about 300 gm. of sugar in his urine each day. The therapy was continued, but he was also given IABG, 200 mg. four times a day, and during the next month he had no glycosuria. After this, insulin was gradually reduced and then completely discontinued after two months on biguanide therapy. He was changed to PEBG, 100 mg. four times a day, and on this drug, too, his urine remained sugar-free. The dose of PEBG was decreased to as little as 100 mg. twice a day, and it was discontinued on Aug. 9, 1957. On Aug. 13, all urine yielded a 4+ sugar reaction. On Aug. 15, 1957, a 24-hour urine contained 43.6 gm. of glucose and so ABG therapy was resumed. On 100 mg. four times a day, and later on 125 mg. four times a day, he became somewhat anorectic and his urines all yielded 3+ or 4+ sugar reactions. Thirty units of isophane insulin was given, but even this, plus 125 mg. of ABG four times a day, did not control this patient. After one and one-half months of this combined therapy, which had proved to be inadequate, PEBG alone was prescribed in doses of 100 mg. four times per day. This has controlled him perfectly well, and his urines are again negative. Further definitive treatment of his acromegaly is planned.

Case 5. (Adult-Onset Diabetes).—A 56-year-old man who had had diabetes for 10 years had been well controlled on 50 units of isophane insulin a day. This was reduced to 40 units, and ABG therapy was started at 50 mg. four times a day. Urine, tested for sugar four times per 24 hours, showed no change on this therapy. ABG dosage was raised to 75 mg. four times a day, and insulin was lowered to 20 units. All urine sugar reactions became 3+ to 4+, and the patient became anorectic and severely nauseated. He vomited once. The dosage of ABG was decreased to 50 mg. four times daily, and insulin was increased to 30 units daily. Twenty-four hours after the initiation of this regimen the patient felt perfectly well. Tests for sugar in the urine yielded 2+ to 3+ reactions, and one week later ABG therapy was discontinued.

Two weeks later this patient was treated with PEBG, with doses up to 350 mg. a day; the results were the same. Anorexia and nausea occurred, though this time there was no vomiting. All physical findings, hematocrit, white blood cell count, blood urea nitrogen, cephalin flocculation, and sulfobromophthalein excretion tests remained at their pretreatment levels. The patient is again being controlled on isophane insulin.

Case 6 (Adult-Onset Diabetes).—A man aged 54, a chronic alcoholic, had had diabetes for three months and was controlled on 40 units of isophane insulin. Insulin was stopped in March, 1957, and the patient was eventually regulated on IABG, 200 mg. four times a day. The blood sugar on this regimen was found repeatedly to be between 120 and 165 mg. %; urine sugar tests, conducted four times daily, were usually negative or, rarely, 1+ to 2+. In July, 1957, he went on a three-day alcoholic spree and returned to the hospital in acidosis; the blood sugar value was 684 mg. %, and the blood acetone test showed a 4+ reaction. His blood CO_2 combining power was 4 mEq. per liter. Forty units of regular insulin intravenously sufficed to reduce his blood sugar to 43 mg. % and to increase the CO_2 to 24 mEq. per liter. This time the patient was discharged on PEBG, 100 mg. three times per day. He experienced anorexia and vomiting on this dose, and so for one week he was controlled on 35 units of isophane and 15 units of regular insulin. He was then treated with ABG, 100 mg. four times daily; this regimen has controlled him well. In order to evaluate therapy, we stopped ABG on Sept. 11, and, beginning 48 hours later, the patient noted continual 4+ urine sugar reactions. A fasting blood sugar test showed 280 mg. %. ABG, 100 mg. four times a day, was resumed, and urine sugar tests became negative. Because of a 20 lb. weight loss, occurring mostly during acidosis and mild anorexia, insulin therapy was added, and the dosage of ABG was reduced to 75 mg. four times daily. The patient's appetite increased, and he gained 8 lb. in the following week. He was regulated on 20 units of isophane insulin plus 75 mg. of ABG four times a day. On this therapy he felt well and diabetic control remained excellent. In spite of this he failed to gain any more weight and remained 15 to 20 lb. underweight. After four weeks of this therapy, ABG was discontinued and insulin, reinstituted. Ten days later he had gained 12 lb. and stated he felt much better (although no specific complaints could be elicited while he was taking ABG). He remains well controlled on 28 units of isophane insulin once daily. No change has been demonstrated by means of repeated physical examinations, and the following tests, repeated periodically; sulfobromophthalein excretion, cephalin flocculation, blood urea nitrogen, urinalysis, hematocrit, and white blood cell count.

Comment

The clinical use of the oral biguanide hypoglycemic agents has been presented. All types of diabetes studied, including juvenile, have responded to treatment. Although several diguanidines, such as Synthalin A, produce renal and hepatic necrosis after only one to two days of use, there has been no known histologic damage attributed to the biguanide compounds which we used in our study. It is to be noted (Fig. 1) that Synthalin A and biguanide compounds differ significantly in chemical structure. In many of the patients whom we have treated, significant decreases in blood and urine sugars have been produced, but a relatively high incidence of anorexia, nausea, vomiting, weight loss, malaise, weakness, and some diarrhea have markedly handicapped extensive usage.

The pathogenesis of these side-effects is uncertain. Bodo and Marks [3] reported elevated phosphorus levels in animals treated with Synthalin A and other guanidines. Indeed, inhibition of oxidative enzymes systems [9] might result in a decreased binding of high-energy phosphorus, allowing inorganic phosphorus to escape into the blood stream. So far we have observed no definite abnormalities of calcium and phosphorus in patients on biguanide therapy. The pathogenesis of *late* side-effects (consisting of weight loss, weakness, lethargy, and malaise) has not been explained. Occasionally, in the presence of a constant dietary intake and little or no glycosuria, weight loss might be due to loss of metabolites in the feces or urine. One possibility might be loss of lactic acid in the urine. Studies along this line are in progress also.

We have seen two patients develop acidosis while on biguanide treatment, one during an upper respiratory infection and another after an alcoholic spree. Both patients, when compared to the usual acidotic diabetic patient, seemed unusually sensitive to insulin; each of their blood sugars dropped from 684 and 454 mg. %, respectively, to normal or below on 40 units of regular insulin. One of these patients had a hypoglycemic reaction with a blood sugar of 43 mg. %. We believe that this was due to the effect of the biguanides on hepatic glucose output.

When patients are well controlled on the biguanides there is usually no glycosuria. We have observed no hypoglycemic reactions in the patients on biguanides alone. Five patients had reactions when they were receiving insulin, also, but were relieved when the insulin dose was lowered. Such hypoglycemic reactions responded promptly to administration of carbohydrate, either orally or parenterally.

In general, it was easier to replace insulin completely by a biguanide compound for treatment of diabetes if the insulin dose was relatively low initially (Fig. 2). This is probably related to the fact that lower doses of the biguanides are needed to control a mild diabetic patient than are necessary for a more severely ill one, and more patients can tolerate the low biguanide dose without side-effects. Use of these compounds in the treatment of diabetes is seriously limited by the high incidence of these unpleasant side-effects, but in some patients their use aids remarkably in control of the diabetes.

The long-range effect of the biguanide compounds on diabetic complications is not known. The biguanides may decrease the blood sugar and avert acidosis, only to allow other sequelae to proceed unchecked. However, there is no evidence at present to suggest that this is true. The smoother control afforded by these drugs may augment the power of insulin to lessen such complications. We are currently following a series of patients in order to make long-term evaluation of this method of therapy.

Summary

A preliminary report is presented dealing with the oral treatment of diabetic patients with amyl-, isomyl-, and phenethylbiguanide.

Fifty-two per cent of the patients treated had a "good" response, which was defined

as a decrease of the fasting blood sugar by 30% or more, with at least a 50% decrease in glycosuria or a decrease in insulin requirements 30% or more.

Treatment was hindered markedly by the high incidence of side-effects, and these were of two types: (*a*) Early side-effects consisting of anorexia, nausea, vomiting, or very rarely, diarrhea, usually occurring in the first week of therapy, were seen to some extent, though usually in mild form, in 60% of the patients treated. (*b*) Late side-effects occurred after 4 to 16 weeks of apparently successful therapy in 10 out of 28 patients treated for one month or longer. These consisted of weight loss, weakness, lethargy, and malaise. All side-effects, early and late, generally disappeared from one to three days after the biguanide therapy was discontinued and in all cases were gone within one week. No permanent effects of any kind have been observed, in spite of careful search.

There was no correlation between age of the patient, duration of diabetes and/or insulin therapy, and response to biguanide therapy, but there was an inverse correlation between the dose of insulin necessary to control the diabetes and the per cent of patients responding to biguanide therapy.

Diabetic acidosis occurred in two patients while on biguanide therapy. Their blood sugar level fell to normal or below on remarkably small doses of insulin.

In some cases the severely labile diabetic patient, who could not be controlled on insulin, was well controlled on insulin plus a biguanide.

Most mild diabetic patients were well controlled on a biguanide compound, and such control was occasionally superior to that by insulin. This was true regardless of age, duration of diabetes, or response to tolbutamide.

In many diabetic patients biguanide therapy produced excellent results, but its use was severely hampered by the high incidence of side-effects. Final evaluation must await a more thorough elucidation of its biochemical effects, for it is possible that with such knowledge side-effects might be eliminated while the hypoglycemic effect is preserved.

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Surfeit and Deficit of Sodium

A Kinetic Concept of Sodium Excretion

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Normal man can maintain an over-all sodium balance at intakes varying from a few to 1000 mEq. or more of sodium daily. Although this balance is customarily referred to as a steady state, at all levels of sodium intake higher than a few milliequivalents daily it represents in reality a constantly fluctuating level of total body sodium. Each time sodium is ingested a positive balance is produced which is steadily reduced in the following hours by way of renal sodium excretion. This is well illustrated in a study from this laboratory [1] in which identical meals and quantities of salt were administered to constantly recumbent subjects at six-hour intervals. Figure 1, plotted for the second day of this study, reveals that the sodium ingested at the beginning of each six-hour period has just about been eliminated by the end of the period, save for the night hours, particularly from midnight to 6 a. m., when there is a marked diminution in sodium excretion. The teleological usefulness for man, with his erect habitus, of this nocturnal reduction in sodium excretion, will be commented upon later.

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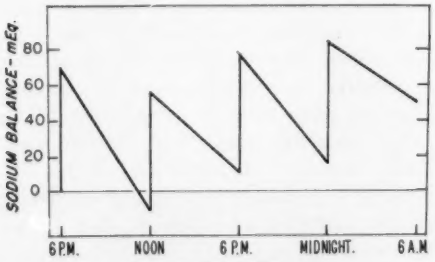

Fig. 1.—Sodium balance, as estimated from dietary intake and urinary excretion, in a recumbent subject receiving an identical intake of food, salt, and water at six-hour intervals throughout the day and night (plotted from the data of Rosenbaum et al.[1]).

Exponential Decrease in Sodium Excretion Following Dietary Restriction

Almost a century ago Carl Ludwig [2] noted that when man, in over-all salt balance upon a fixed level of sodium intake, shifted to a lower level of intake, about three days were required for a steady state to be reestablished and that when this did occur it was at a lower total body content of sodium. It has since repeatedly been observed that when a shift from any given level of sodium intake is made to a very low intake, the *total* sodium excretion during the several days before the urine becomes virtually sodium-free approaches a value generally somewhat less than the previous daily intake and excretion. Nearly half of this total sodium excretion occurs in the first day of the restricted intake. This phenomenon appeared worthy of quantitative examination. Accordingly, men whose 24-hour excretion of sodium and other electrolytes had been measured while they took their customary diets and usual quantities of salt were placed on diets containing less than 5 mEq. of sodium daily.

Seven studies were made on healthy physician subjects, six on patients with

minor dermatologic disorders and two on patients with Addison's disease who were maintained on a *constant* daily dose of adrenal hormone. All three types of subjects exhibited similar responses. Analytic methods employed have already been described from this laboratory.[1]

On analyzing the data of these 15 studies it was apparent that potassium remained unchanged throughout and that the daily sodium excretion of each subject after salt restriction bore a relationship to that subject's sodium excretion before dietary restriction—and this despite the fact that sodium excretion on the last day of regular diet varied among the subjects from a low of 60 mEq. to a high of 300 mEq. The curve relating each day's sodium excretion to the original control excretion appeared to fit the familiar exponential decay curve $Na_t = Na_o\ e^{-kt}$ in which Na_t is the sodium excretion on any day t after dietary restriction; Na_o is the sodium excretion on the last day of regular diet; e is the base of natural logarithms, and k is a constant.

The negative logarithm of the ratio $Na_t : Na_o$ has been plotted in Figure 2. The mean value of k is 0.715, with 95% fiducial limits of 0.687 to 0.743. Since the value $e^{-0.715}$ is approximately 0.5, it is apparent that about one-half as much sodium is excreted on each successive day as on the preceding day and that the total excretion of sodium during its restriction, $(\frac{1}{2}+\frac{1}{4}+\frac{1}{8}+\frac{1}{16}\ldots)Na_o$, approaches Na_o as a limit. As a further check on this over-all calculation, since any large error in Na_o would bias the result, the individual ratios for successive days have been calculated and are 0.49, 0.50, and 0.56, respectively, and thus are in agreement with the general formulation.

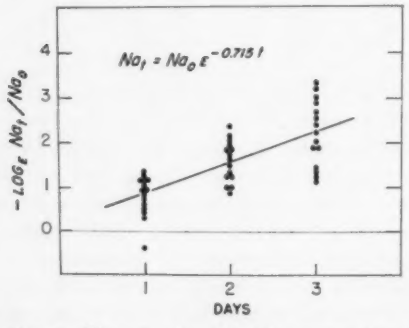

Fig. 2.—Plot of $-log_e\ Na_t : Na_o$ versus time in days for the determination of the regression coefficient of the equation relating daily sodium excretion after restriction of intake to the level of excretion while the subjects were on customary diets. The equation of the regression line is $y=0.118+0.715x$. The standard error of the regression coefficient is 0.028 with $t=25.5$ and 1 degree of freedom.

It is of interest that a similar type of calculation performed on the combined data of Nadal et al., published in 1941,[3] and of Leaf, Couter, and Newburgh, published in 1949,[4] reveals the same type of exponential decline in sodium excretion ($k=0.696$). Black,[5] comparing hypertensive and normotensive persons, also noted an exponential decline in sodium excretion after its dietary restriction, and the same may be inferred from a number of similar reports, such as that of Dole et al.[6]

What is the significance of this exponential type decrease in renal sodium excretion? Since the subjects were capable of excreting, and in fact did excrete, on the last day of the regular diet an amount of sodium equal to or greater than the amount they eliminated during the next three days, it is apparent that there was no primary renal restriction on sodium output which prevented the excretion of the entire amount on the first day of restriction.

An alternative hypothesis which might be advanced to explain the failure of the urine to become virtually free of sodium until several days after institution of the very low sodium intake is that this length of time is required for sodium-conserving mechanisms to come into full action (or for a sodium-excreting mechanism to become completely inactive). In order to test this hypothesis we planned to force the excretion, on the first day of restricted diet, of an amount of sodium equal to or greater than the previous daily excretion by either an extrarenal route or through the employment of a mercurial diuretic. If several days were required for some mechanism to become fully active or fully inactive, then the

amount of sodium lost on the first day should not affect sodium excretion on the next few days. We were pleased to recall that a fine experiment somewhat of this type had been performed, although for another purpose, a quarter century ago by Blumgart and his associates.[7] Normal subjects were maintained on rigidly controlled neutral diets, adequate in all respects, given at specified times each day, the subjects receiving the same articles of food and quantity of salt every day. Water intake and water content of the diet were uniform daily. Studies were commenced only after the subjects had been on the regimen for at least a week.

We have plotted the data concerning sodium excretion (Fig. 3) for one of the subjects who, on the day he received 2 ml. of merbaphen (Novarsurol), excreted almost three times as much sodium as he had on any of the preceding days. On the next two days only minimal amounts of sodium appeared in the urine despite the continued ingestion of 75 mEq. daily, thus clearly demonstrating that when the loss of sodium is large enough to result in depletion, adequate renal sodium conservation occurs within 24 hours. Inspection of the two charts illustrating Hilton's study[8] of mercurial diuresis in normal subjects receiving 100 mEq. of sodium daily also indicates that when sodium excretion following mercurial injection was approximately three times the intake, immediate renal conservation ensued. A somewhat similar observation has recently been made in this laboratory[9] on a subject who excreted 320 mEq. of sodium as a result of a mercurial diuretic and then, on a diet containing less than 10 mEq. of sodium daily, excreted 7, 3, and 2 mEq. daily during the next three days. These observations then—and there are no doubt many similar ones hidden in the literature on diuretics—dispose of the hypothesis that the major sodium-conserving mechanisms are so sluggish as to require several days for complete activation.

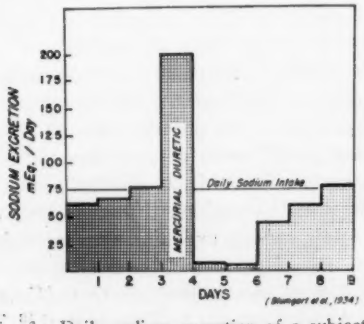

Fig. 3.—Daily sodium excretion of a subject receiving an identical daily intake of food, salt, and water before and after injection of 2 ml. of merbaphen (plotted from the data of Blumgart et al.[7]).

A third hypothesis—the one which we favor—is that the amount of sodium excreted in the urine in any one day is a function of total body sodium on that day and particularly of that moiety which is in excess of the body's needs. Thus we would assume that a person ingesting 200 mEq. of sodium daily and excreting 200 mEq. daily in the urine is doing so because that amount is surplus to his needs and is being maintained in the body only by continued ingestion. If this ingestion ceases, then as the surplus sodium in the body decreases, so pari passu would its rate of excretion, and an exponential decay type of curve would be anticipated.

Response of Sodium-Restricted But Not Sodium-Depleted Person to Administration of Minute Amount of Sodium

After a normal subject has been maintained for three or four days on a diet containing less than 5 mEq. of sodium daily he reaches a steady state insofar as sodium is concerned in which his daytime urinary sodium excretion is reduced to a few microequivalents per minute and the total daily excretion is less than the intake, presumably because of small, but unavoidable, extrarenal losses.

At such a time the response of the person to the challenge of a small increase in total extracellular fluid sodium,* of the order of

* Total extracellular fluid sodium has been estimated at 1700 mEq. for a 70 kg. adult. Total body sodium may well be more than twice this quantity.[10]

less than 1%, might be most revealing as to the kinetics of sodium excretion in man. Accordingly 10 such studies were made. In each case the challenging infusion consisted of 150 ml. of a 0.6% sodium chloride solution. Such a solution, containing 15 mM. of sodium chloride at a concentration of 100 mEq. of each ion per liter, could not conceivably elevate the serum level of either ion. Since there is ordinarily an early morning increase in sodium excretion after arising,[1] the experiments were never conducted until late morning, and in order to eliminate the effect of any type of diurnal variation, they were scattered from late morning to late afternoon without in any way influencing the results.

The subjects were either healthy physicians or patients with minor dermatologic disorders. For three or more days preceding the study they had been partaking of a diet containing less than 5 mEq. of sodium daily. Several hours after a virtually sodium-free breakfast or light lunch, the subject drank 500 to 1000 ml. of tap water to ensure an adequate urine flow and to eliminate difficulty in timed voiding and assumed a fully recumbent position in bed. Urine specimens were obtained at half-hour intervals thereafter, the subject standing to void on each occasion. At the end of two hours, venous blood was collected without stasis from an antecubital vein and the aforementioned infusion commenced intravenously at a rate of approximately 10 ml. per minute so that the total amount was infused within 15 minutes. Spontaneous voiding at half-hour intervals was continued for the next four hours. At each voiding the subject drank an amount of tap water equivalent to the volume of urine passed plus 40 ml. per hour for estimated insensible loss. Throughout the entire period each subject ingested 5 gm. of sucrose every half hour in order to avoid the effect of carbohydrate depletion on sodium excretion.[11] The results are depicted in Figure 4. Sodium excretion, which averaged 18μEq. (microequivalents) per minute during the hour and one-half prior to the

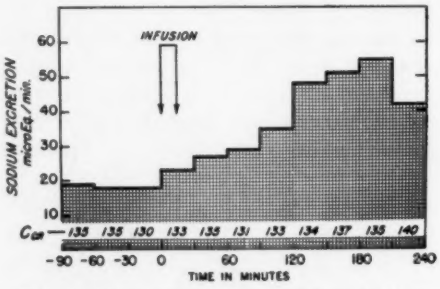

Fig. 4.—Mean renal sodium excretion in 10 recumbent sodium-restricted but not sodium-depleted subjects before and after the intravenous infusion of 15 mM. of NaCl in hypotonic solution. Endogenous creatinine clearance is shown in lower figures.

infusion, commenced to rise during the first half hour (including the 15-minute period of infusion) and continued to do so until the fourth hour, when it reached an average value of 56μEq. per minute, or approximately a threefold increase. By the end of four hours, at which time the studies were terminated, the total amount of sodium excreted above the control excretion averaged 5.5 mEq., or slightly more than one-third of the challenging dose of sodium. Control studies, in which an identical procedure was followed, including the collection of venous blood, but without a saline infusion, showed that there is no tendency for sodium excretion to increase spontaneously after two hours of recumbency.

For purposes of contrast it is of interest to consider the response of a person who, ingesting 140 mEq. daily of sodium, was challenged by an infusion of isotonic (0.9%) sodium chloride solution of such a magnitude (2200 ml.) that 338 mEq. of sodium was administered during a period of approximately 100 minutes—a total amount more than 22 times greater than our challenging infusion and administered more than three times as rapidly. Figure 5 contrasts the mean sodium excretion of our subjects with, on a scale ten times as great, the response to the larger infusion (Case 6, Fig. 4) administered by Papper et al.[12] The similarity of response both in time and in relative magnitude is obvious. During the

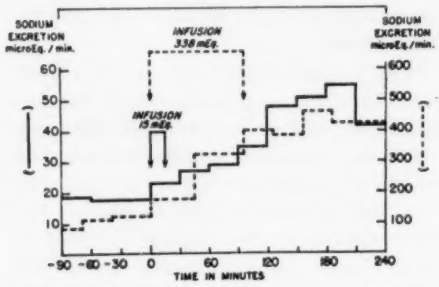

Fig. 5.—Comparison of the mean renal sodium excretion following challenge of 15 mM. of NaCl in 10 sodium-restricted subjects with the response of the subject of Papper et al.,[12] who received 338 mM. of NaCl in isotonic solution. Scale on right for subject of Papper et al. is 10 times that of scale on left for the sodium-restricted subjects.

four-hour period of observation, Papper's subject excreted 20% of the administered dose, as compared to 30% of the infinitely smaller dose given in the present studies.

Endogenous creatinine clearance, employed as an index of glomerular filtration rate, shown at the bottom of Figure 4, did not change significantly throughout the study. Potassium excretion decreased progressively throughout the four hours after administration of the challenging infusion, as it did in control studies in which no infusion was given. Chloride excretion, which averaged 24μEq. per minute during the control period, declined slowly to an average value of 15μEq. per minute after the infusion, again similar to the control studies without infusion.

These observations, then, indicate that when recumbent man, in a steady state with regard to sodium, at a *very low level of intake,* receives additional sodium by way of an intravenous infusion of a minute quantity of sodium chloride in hypotonic solution—so as not to raise the plasma level of either ion—he promptly increases the rate of urinary excretion of sodium and within a period of four hours disposes of almost a third of the challenging load, if indeed 15 mM. of sodium chloride can be called a "load."

It is difficult to conceive of any bodily mechanism which could become apprized of the fact that there was a less than 1% increase in the amount of salt in the body except by an increase in sodium or chloride concentration in the body fluids or by an increase in the volume of these fluids. The former has been excluded on the grounds that the infused solution contained sodium and chloride at a lower concentration than the serum. Obviously an increase in the volume of the body fluids has occurred, presumably largely restricted to the extracellular fluid by virtue of the fact that sodium and chloride are for the most part excluded from cells.

Absence of Response of Sodium-Depleted Person to Sodium Administration

The ability of the normal kidney to elaborate a virtually sodium-free urine, added to the fact that the dietician's best efforts can hardly provide a satisfactory diet that does not contain at least a few milliequivalents of sodium, makes it impossible to deplete the body of sodium save by promoting its extrarenal loss or by forcing its renal excretion through poisoning the renal tubular cells or otherwise. The latter method of depletion, as noted above, employed by Blumgart et al.[7] and Hilton,[8] led to the elaboration of a virtually sodium-free urine despite the fact that the subjects ingested 75 and 100 mEq. of sodium, respectively, daily. The extrarenal method of sodium depletion was employed by McCance, in 1936.[13] In an exquisite series of balance studies, he accomplished a net loss of 758 mEq. of sodium in himself, in part by renal excretion but mostly through induced sweating. His urine became virtually free of sodium (less than 1 mEq. per day). When he began sodium repletion, he ingested 498 mEq. during the first two days. The urinary excretion on these days remained at 1 mEq. On the third day he ingested enough sodium to make the three-day total intake 732 mEq. On that day 16 mEq. of sodium was excreted in the urine.

Our experiments lack the elegance of the measured balance studies described. They were performed merely to make sure that

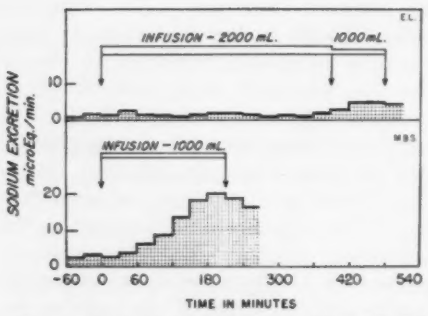

Fig. 6.—Lack of response of a subject (E. L.) considerably *depleted* of sodium, to the intravenous infusion of 200 mM. of NaCl in hypotonic solution and minimal response to the additional infusion of 100 mM. (upper chart). Delayed and slight response of a mildly *depleted* subject (M. B. S.) to the infusion of 100 mM. of NaCl in hypotonic solution.

the route of administration of sodium and its concentration were not significant and to afford a contrast to the studies on the sodium-restricted but not sodium-depleted subjects. The procedure was simple. After a number of days upon the less than 5 mEq. daily sodium intake and after one of the studies previously described the subject (E. L., Figure 6) proceeded to soak in a hot tub (105 F) for an hour a day for three days, immersing himself to the extent that his oral temperature was maintained at an average level of 101 F, and sweating occurred. A weight loss of 2 kg. ensued. The minimal dietary intake of salt was continued. On the day after the last sweat an intravenous infusion of 0.6% sodium chloride solution was commenced at the rate of 5 ml. per minute and half-hourly urine collections secured by spontaneous voiding. After six and one-half hours, the renal excretion of sodium not having risen above 2μEq. per minute and 2 liters of the solution (200 mM. of NaCl) having been administered, the rate of infusion was increased so that a third liter (an additional 100 mM. of NaCl) was given within 90 minutes. This increased the rate of sodium excretion to 5μEq. per minute (Fig. 6). The same subject, when sodium-restricted but not sodium-depleted, exhibited a prompt increase in sodium excretion when he received only 150 ml. of 0.6% sodium chloride solution.

The second subject (M. B. S., Fig. 6) after similar dietary preparation as the first, limited himself to one day's hot bath under the same conditions. On the following day his basal sodium excretion of 3μEq. per min. did not increase until he had received over 400 ml. of the infusion (40 mM. of NaCl) and reached a peak rate of only 20μEq. per minute after 1000 ml. of the solution (100 mM. NaCl) had been given. He also had had a prompt response to 150 ml. of 0.6% sodium chloride solution when sodium-restricted but not sodium-depleted.

The above observations, then, indicate that when sodium depletion has been accomplished through the promotion of forced renal sodium excretion (mercurial diuretics) or extrarenal sodium loss (sweating), administered sodium chloride is retained quantitatively until the bodily deficit of sodium has been restored, after which any further sodium administered is handled as if surplus to the body's needs.

Comment

The many factors which may influence the renal excretion of sodium in normal man, such as solute and anionic loading, dehydration, and disturbances in acid-base equilibrium, have recently been reviewed [14] and require no elaboration here. The conditions of the experiments reported in the second section were such that many of these factors may confidently be excluded from consideration. Furthermore, these conditions, save for the absence of the challenging infusion, were identical in the control studies.

Since sodium excretion is believed to represent the amount of filtered sodium which is not reabsorbed by the tubules, an increase in the filtered load could explain the enhanced sodium excretion. The infusion contained both sodium and chloride in lower concentration than the plasma. Thus it is improbable that it increased the filtered load by raising the concentration of either ion

in the glomerular filtrate. The load could have been increased if glomerular filtration rate rose. No such increase could be detected with use of creatinine clearance as an index of filtration rate. The infusion of any extraneous substance, such as inulin or mannitol, for the measurement of filtration rate would obviously have defeated the purpose of the experiment. Furthermore, with the best of methods and techniques the errors involved are far greater than the magnitude of change which conceivably could have led to the increase in sodium excretion, since a less than 1% increase in glomerular filtration rate would lead to an increase of approximately 140μEq. per minute in sodium delivery to the tubular system. Since the maximal increase in sodium excretion was delayed for several hours, the hypothesis that this enhanced sodium excretion was due to an increase in filtration rate would demand acceptance of a second hypothesis, that is, that an infusion of 150 ml. of hypotonic saline solution produces its maximal effect on filtration rate only after several hours.

On the other hand, if the increase in sodium excretion is ascribed to diminished tubular reabsorption as the result of inactivation of a sodium-retaining system or the activation of a sodium-excreting system,[15] just such a delay might be anticipated. As a working hypothesis we favor such a concept, since the alternative seems to lead to an impasse presently incapable of solution.[16]

The possible mechanisms involved in the renal response to changing levels of extracellular fluid volume have recently been extensively reviewed.[17,18] We are in complete agreement with Dr. Homer Smith's concept that body fluid volume regulation centers on sodium chloride and that sodium rather than chloride is specifically reabsorbed by the tubules.[17] The precise mechanisms are obscure, although the bulk of the evidence suggests that there is a critical area or areas located cephalad (not necessarily within the head) responsive to some function of extracellular (probably interstitial) fluid volume.

The role of the adrenal cortical hormones, and particularly of aldosterone, in the observed phenomena demand consideration. In a recent discussion [19] it was pointed out that although there is a reciprocal relationship between urinary aldosterone and renal sodium excretion following manipulation of the volume of extracellular fluid, correlation does not signify causality. Both aldosterone excretion *and* sodium excretion may be responsive to the same stimulus without the one being directly related to the other.

The two subjects with Addison's disease, in whom the absence of endogenous adrenal hormone secretion may be presumed, exhibited the same exponential type of decrease in renal sodium excretion that the other 13 subjects did. Rosenbaum, Papper, and Ashley [20] have shown that patients with Addison's disease exhibit the same responses in renal sodium excretion following alterations of the extracellular volume as do normals. Epstein [21] has demonstrated the same phenomena in an adrenalectomized patient. Thus at the moment there is no compelling evidence implicating aldosterone or any other adrenal cortical hormone in the observed events, and we cannot but feel that a search for mechanisms in other areas might be fruitful. The exquisite sensitivity of the sodium-restricted but not sodium-depleted subject to alterations in the extracellular fluid volume should make such persons ideal for further investigation of the mechanisms involved.†

Oversimplification

In Figure 7 we have endeavored to depict, in oversimplified fashion, our concept of the kinetics of renal sodium excretion in the adequately hydrated *recumbent normal human subject.* Extracellular fluid (ECF) volume, scaled on the left, is considered to be a function of total extracellular fluid sodium, scaled on the right so that 140 mEq. of sodium is equivalent to 1000

† As well as for other purposes, such as the comparative evaluation of diuretic agents.

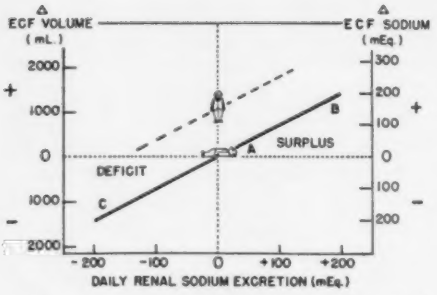

Fig. 7.—An oversimplified diagram of the kinetics of renal sodium excretion in the adequately hydrated, recumbent, normal human subject. See text for explanation.

ml. of ECF. Such a correspondence appears to hold under circumstances in which serum sodium concentration remains constant.‡

Sodium excretion has been charted as abscissa and includes *negative* values, an artificiality designed to indicate the amount of sodium which must be administered to a depleted person before there is any renal sodium excretion.

Just to the right of the intersection of the two axes (*A*) is the state of the 10 subjects who had been sodium-restricted so that their urine contained minimal amounts of sodium and in whom a tiny increment in body sodium (and ECF volume) immediately increased renal sodium excretion.

To the right (*B*) is the state of most normal humans ingesting customary diets and usual quantities of salt; it is a state of equilibrium only when viewed over a period of hours or days. During any short period of time it represents a fluctuating level as shown in Figure 1. In the absence of salt ingestion the state of the subject approaches *A*, reaching there after several days. To be sure, one could no doubt achieve a steady state at point *B* by the constant minute-by-minute administration of sodium. It is to be emphasized that the fact that a surplus of 200 mEq. exists at any one time does not mean that in the absence of repeated salt administration the subject will excrete 200 mEq. in the urine in one day, for in the absence of such salt intake each moiety of sodium excreted will diminish the amount of surplus, decrease the excretory rate, and move the subject's state toward position *A*.

To the left (position *C*) is the state of the sodium-depleted subject who excretes no sodium until the deficit has been repaired.

It will be noted that an erect figure has been sketched lightly, with a regression line placed parallel to but in a higher position than for the recumbent subject. This is to suggest that a quantity of sodium or a volume of ECF that is surplus in recumbency and subject to excretion may represent a deficit when the subject is in the erect position. It may well be that despite his assumption for thousands of years of the erect posture during most of his waking hours, man has not yet accomplished a completely adequate adjustment to this position but remains somewhat ambivalent and when on a very low salt intake retains sodium when erect and rejects it when recumbent. Possibly this constitutes one of the reasons why habitual consumption of salt far in excess of any reasonable requirement is so common among humans. Archaeologic evidence as well as history indicate that man has been fond of salt for thousands of years, although many instances can be cited of tribes to whom the use of salt was either unknown or distasteful.[23] Nevertheless one may infer from the present-day habits of the anthropoids that our own ancestors at one time subsisted largely on roots and shoots, nuts and fruits, and obtained a very minimal intake of sodium.[24] In fact Forde[25] has ascertained that the Semang of central Malaya subsisted on such a diet in recent times and that the southern Paiute did likewise before being displaced by white men.

‡ One can expand the ECF by forced hydration and vasopressin injection[22] without increasing its sodium content, and one can contract the ECF by dehydration without necessarily diminishing its sodium content. One may also redistribute extracellular fluid by sitting or standing, by the application of tourniquets, and by other maneuvers, but none of these is involved here.

The nocturnal decrease in sodium excretion previously alluded to, a very persistent phenomenon despite experimental endeavors to disrupt it,[26-28] may have served our remote sodium-restricted ancestors in good stead. Without it they might well have excreted so much sodium while recumbent at night that upon assuming the erect posture in the morning they would suffer from an actual deficit. Not until primitive man advanced from the anthropoid type of vegetarian diet to the hunting and fishing stage and obtained sodium from the extracellular fluid of his prey could he have been on more than a minimal intake of this element in most geographic locations. Indeed it has been suggested that the development of the human brain and present-day civilization may be correlated with man's salt-gathering. But then, too, so has hypertension and arteriosclerosis!

Conclusions

An equilibrium state insofar as the body content of sodium is concerned may exist under three sets of circumstances:

1. There may be a surplus of sodium in the body, as is the case in most normal persons ingesting their customary intake of salt. In this condition, sodium is continually being excreted in the urine and a constant amount of sodium in the body can only be achieved by continual salt ingestion.

2. There may be a deficit of sodium in the body, as is the case when sodium excretion has been forced by extrarenal routes or mercurial diuretics. In this condition, in the absence of sodium intake the body content of sodium will remain constant but sodium is virtually excluded from the urine and does not reappear until the deficit has been made up.

3. There is, between the states of surplus and deficit, a condition in which the body sodium remains steady as long as there is a minimal intake of sodium sufficient to make up unavoidable (and largely extrarenal) losses. In this condition, the addition of a minute increment to the body content of sodium leads to an immediate increase in renal sodium excretion.

It is believed that the regulation of renal sodium excretion under all these circumstances is determined by a function of the volume of extracellular fluid in some critical area or areas of the body and that this in turn is largely a function of the bodily content of sodium.

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The Epidemiology of Psittacosis and Report of a Turkey-Borne Outbreak

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The increasing number of cases of psittacosis reported in the United States has been attributed to less stringent restrictions on the sale of psittacine birds [1-4] and to the increasing popularity of the parakeet as a household pet. The number of cases reported to the National Office of Vital Statistics have increased each year since 1951, when the United States Public Health Service related the interstate and foreign quarantine regulations for the importation of psittacine birds.[1] While psittacine birds are probably the commonest source of human psittacosis, many other species of birds have transmitted the infection to man. Pigeons, ducks, chickens, turkeys, canaries, sea gulls, egrets, and even "road runners" (chaparral birds) have been found to harbor the infection.

It is the purpose of this paper to review the history of the epidemiology of the disease and to report an epidemic occurring in two turkey-processing plants in Houston, Texas.

1. Epidemiology of Psittacosis

Historically, the first clearly recorded description of the epidemiology of this disease was made by Ritter,[6] a practitioner in Uster, Switzerland, in 1880. He observed a house epidemic of pneumonia accompanied by a typhoid state involving seven persons, three of whom died. The illness began in five members of his brothers' family 24 to 26 days following the arrival of six birds from Hamburg, which were placed in a room where exotic birds were kept. One of these birds became ill and died, but the temporal relationship between this and the patients' illnesses is not recorded. Only two patients were not permanent residents of the house, one being a carpenter who was in charge of enlarging the bird cages and the other, a clerk who was in the room on two occasions. These two patients had incubation periods 10 days longer than the others.

In two patients, the only exposure was 14 days after receipt of the birds. Ritter believed that this date was the date of dissemination in all those infected and consequently that the incubation period was about 10 days in five patients and about 20 days in the other two. The patients "all complained of headaches, fatigue, persistent chills and no appetite." Autopsies on the patients who died revealed evidence of pneumonia. From the epidemiological and clinical data he recorded, it seems certain that this was an epidemic of psittacosis, although it was called "pneumotyphus."

In 1884, E. Wagner [7] described nine cases of "so-called pneumotyphus." Of these, one person was exposed to monkeys and parrots, two persons came from families where typhoid fever was present, and all the others were exposed to dogs. Again [8] in 1888 he described three cases, all of which had been exposed to exotic animals, type unspecified. Outbreaks similar to those of Ritter were described by Ost.*

The first major outbreak of psittacosis occurred in 1892 in Paris, following the shipment of 500 parrots from Buenos Aires.[9-11] Only 200 of the birds reached Paris; the others died in transit. Of those

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* Cited by Hutchison.[9]

persons coming in contact with the birds, 49 became ill with pneumonia and 16 of these died. Nocard,† the famous French veterinarian, was commissioned by the French government to investigate this outbreak. From the wing bone marrow of dead birds he was able to isolate a Gram-negative, short, motile, bacillus which did not liquefy gelatin, ferment lactose, or coagulate milk and which when inoculated into other parrots would produce fatal septicemia within 48 hours. Further, he was able to infect normal birds by placing the dried wings of diseased birds into the cages; consequently, he concluded that this bacillus was the causative agent of this disease.

It was during this epidemic that Peters ‡ labeled the disease *typhus des perruches,* while three years later Morange,[12] reviewing this outbreak, suggested the name "psittacosis."

Smaller outbreaks occurred in 1893 and 1894. In 1896, again in Paris, Gilbert and Fournier [10] observed a small house-epidemic in which seven persons were ill and two died. For the first time, the Nocard bacillus, or Salmonella typhimurium (Bacillus psittacosis), was isolated from a patient, from the heart blood at postmortem examination. In addition, they demonstrated agglutination of the organism when subjected to the Widal reaction,[11] although it required a greater concentration of serum.

Scattered local outbreaks occurred throughout Europe over the next several years. The first cases recorded in the United States were reported by Vickery [13] in 1904 from New Hampshire, where three people were involved in a house-epidemic. The first major epidemic in the United States was in Wilkes-Barre, Pa., and was investigated by A. T. McClintock.[14]

"On March 2, 1917, a large number of parrots arrived in Wilkes-Barre. They were exhibited for sale, grouped together in the open in a department store. Many were ill when they arrived. A large number soon died. Great crowds came to see the parrots, 48 were sold and taken to homes, a number died, some recovered, some never appeared ill. The parrots were in the store 48 hours and were then sent on.

"In about 10 days, the sick list of the store employees began to grow. At about the same time, many peculiar cases of illness appeared in the practices of physicians in Wilkes-Barre and the surrounding towns. The patients usually gave a clear history of contact with the sick parrots, either at the store or at home.

"The cases were variously diagnosed as influenza, pneumonia, and very often as typhoid fever. In a little while, the diagnosis of psittacosis was suggested by a clinician. Although certain cases fitted exactly the accepted symptom grouping of this disease, as a whole the clinical picture in this epidemic varied more than in those epidemics previously described, and the mortality was distinctly lower, not above five per cent. The incubation period appeared to be about ten days.

"The parrots had been located in two places, a show window, and in the basement in the center of a large area. A careful analysis was made of the clerks located near the parrots, including one who had charge of those birds which were ill. These individuals were compared in groups for the incidence of the disease. Like the public, practically all the clerks made a point of seeing the parrots. Some people touched the parrots, but in the vast majority of instances, the inspiration of the air of this zone was the common factor.

"As far as could be determined, the disease was not, in its epidemic form, transmissible from human being to human being."

McClintock [14] studied 13 of the cases personally, and there was only 1 death among these. He was able to isolate a Gram-negative bacillus from the blood and sputum of some patients but was unable to demonstrate convincing evidence of agglutination of the organism with convalescent serum.

† Cited by Gilbert.[10]

‡ Cited by Widal.[11]

In June, July, and August, 1929, an epizootic of psittacosis occurred among the parrots in Argentina in the cities Cordoba, Taucumen, and Alta Garcia.[15-17] There were at least 64 cases in addition to 12 deaths in Argentina. These cities were all centers for trading in tropical birds and had a large export trade in birds. From the exportation of birds from this area, cases developed in England, Austria, France, Czechoslovakia, Germany, the Netherlands, Brazil, Denmark, Switzerland, Japan, and the United States.[15,18-20,22,29] Between 350 and 400 cases were reported from these countries during this epidemic,[15] with a mortality of 35% to 40%.

As a result of this world-wide epidemic and failure to find consistent agglutination reactions or isolations of S. typhimurium from human cases,[24,25,28] the etiology of the disease was again studied. Bedson, Western, and Simpson,[26] in February, 1930, were able to isolate a virus from the filtrate of organ suspensions of parrots responsible for human outbreak. In addition, they were able to infect budgerigars with citrated blood, blood serum, and pleural exudate from patients with the disease. Unfiltered suspensions of infected organs heated to 100 F for 20 minutes did not produce illness.

Levinthal,[27] in Germany; Gordon,[28] in London, and Krumwiede, McGrath, and Oldenbusch,[29] in the United States, also transmitted the virus from man to parrots and mice in 1930. Coles,[30] supplied with animals, with blood films from human cases, and with blood and tissue films from infected animals by Dr. Western, was able to demonstrate small coccoid bodies staining red with Giemsa stain. Levinthal[27] also described the presence of specific elementary bodies in the endothelial cells of infected animals, as did Lillie[31] in the United States. Almost simultaneously Rivers[32,33] isolated the virus from a laboratory worker who became infected and demonstrated that parrots, mice, guinea pigs, rabbits, and monkeys could all be infected in the laboratory.

The development of a satisfactory complement-fixation reaction by Bedson,[34] in 1935, provided a simple method for establishing the diagnosis clinically.

The next major epidemiological discovery was the presence of virus in other bird species and the development of human illness from exposure to nonpsittacine birds and possibly from mammals. Wagner[7] in 1884 had reported cases of "pneumotyphus" in which the only epidemiological exposure had been to dogs. Thomason and Hillier[25] reported 21 cases of psittacosis in 1930 and described 1 case in which the exposure was to pigeons. These human cases have been reported to be associated with exposure to pigeons, chickens, pheasants, and turkeys. Pollard[40] has isolated ornithosis virus from a wide variety of seashore birds, although human cases attributable to this source are lacking.

In December, 1942, an outbreak of severe pneumonitis began in the bayou region of Louisiana and ultimately resulted in 8 deaths among 19 recognized cases. The wife of a muskrat trapper was the initial patient from whom the disease spread to the husband, her nurse, and a patient in an adjacent room in the sanatorium. The husband, wife, and nurse all died. From this start, 15 additional cases resulted, in all of which there had been close contact with a diseased patient. The disease spread only to those who had attended fatal cases during the 48 hours prior to death. There was no spread from nonfatal cases.[41]

The origin of the epidemic was never discovered. No patient had been exposed to psittacine birds. The etiological agent,[42] a virus of the psittacosis-ornithosis group, was isolated from three cases.

The determination of the significance of other animal reservoirs has become complicated by the isolation from a variety of mammals viruses which are closely related morphologically and immunologically. Now added to the lymphogranuloma-psittacosis

group are mouse pneumonitis virus (Nigg and Eaton [43]), feline pneumonitis virus (Baker [44]), and bovine encephalomyelitis virus (York [45]). The relationship of animal infections due to the organisms and the spread to birds and to humans has not been finally established.

A human carrier state has been observed by Meyer [46] in which a person proved to harbor psittacosis virus in the secretions of the upper respiratory tract over a 10-year period. Although the virus could be isolated from the sputum, there were no human cases which could be traced to him. The spread of infection from human being to human being has not been of great importance in most reported outbreaks; however, in the epidemic of Louisiana, pneumonitis (ornithosis) was the predominant mechanism of dissemination. This was also commented upon during the 1883-1884 epidemic at Berne, Switzerland, as quoted by Roubakine [15]:

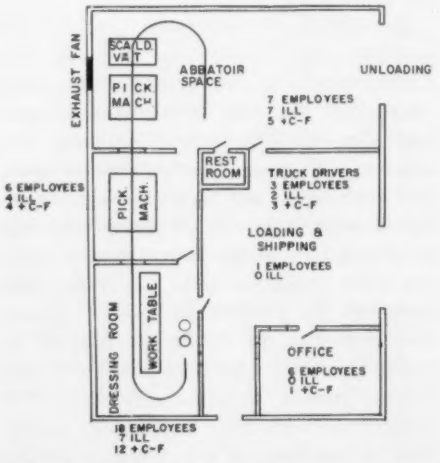
"It was at the clinic at Berne in the charge of Professor Lichtheim. The nurses in attendance on these pneumonia patients —for the disease took the form of an infectious pneumonia—died like flies, one succumbing after another. Rightly or wrongly, it was thought that the only preventive was an excess of cognac!"

Although psittacine birds are responsible for the majority of small "house-epidemics," psittacosis as an occupational disease among poultry-processing-plant workers, especially among those working with turkeys, has become important in Texas. Between 1948 and 1952 there were five outbreaks among poultry workers, with 7 deaths among 96 infected persons. Between 1952 and 1954, there were 264 cases of psittacosis reported to the Texas State Department of Health; 201 of these were reported in 1954, and 190 of these were attributed to dressing turkeys. The source of infection in the turkey is not clear. The failure to isolate the virus from young polts or dead turkey embryos seems to point against transovarian passage. It was theorized that the flocks had become infected while feeding with wild birds; however, examination of wild turkeys, English sparrows, doves, and pigeons during 1954 did not yield ornithosis virus.

2. Epidemiology of 1956 Outbreak in Houston, Texas

On Aug. 28, 1956, approximately 2500 turkeys were brought to Houston from a farm 11 miles north of Waller, Texas, a farm community 60 miles west of Houston with many turkey ranches. The birds were processed by two poultry plants before Sept. 1. The week following delivery of the birds a febrile illness began appearing among the workers in the two processing plants. The floor plan and distribution of employees of Plant A is presented in the Figure. Of the 41 employees of this plant, symptoms consistent with psittacosis were found in 20 and a rising titer of complement fixing antibodies were demonstrated in 13.

Only one sample was obtained from two patients, and in three others a sample was hemolyzed or anticomplmentary. Most of these patients improved promptly after the institution of tetracycline therapy. One patient of this group did not seek medical



The floor plan and distribution of employees of Plant A.

aid until the symptoms had been present for a week and died five days later, despite intensive antibiotic therapy. (The clinical findings in this and another case are the subject of a separate paper.)

The grouping of employees as demonstrated in the plant diagram (Figure) represents the assigned areas of work; however, there was frequent shuffling of employees from area to area with changes in the work load. The only personnel relatively isolated from direct contact with the birds were the office employees, among whom no person developed symptoms, although one person had a rising complement-fixation antibody titer. The group with the highest attack rate worked in the unloading and picking areas, where fluttering of wings stirred dust from the drippings and feathers. The patient who died was employed in this area and in addition was janitor for the plant and killed the birds.

Employees in the dressing room received the birds free of feathers, except for some small pinfeathers. In this area the birds were eviscerated, and, in contrast to the picking areas and abbatoir area, which were dry, the floor in this room was kept wet.

There were 40 employees in Plant B. These persons were not studied as thoroughly as those in Plant A; however, there were 11 persons with clinical symptoms of psittacosis and with positive complement-fixation tests.

Following the onset of illness of the plant employees, the turkeys were impounded by Texas State Health Authorities. The birds had been placed in cold storage for the Thanksgiving market, and none had been sold to retail outlets.

An investigation of the farm from which the turkeys were shipped revealed that there were originally 11,000 in the flock. These had been purchased from a hatchery on three separate occasions and were separated into three different groups according to age.

The oldest group was composed of 5000 birds; the middle group, of 3000, and the youngest group, of 3000. The middle group was entirely isolated from the other two groups. The older and youngest groups were separated only by a wire fence, through which the birds frequently intermingled. Turkeys from the oldest group were shipped as follows: 2500 to a wholesale produce plant in Houston and 1000 to a wholesale produce plant in Dallas.

Apparently some of the birds had not appeared normal at the time of shipping, and when the flock was inspected many of the remaining 1500 turkeys in the older group had become sick and some had died. However, the birds in the middle and younger groups were healthy.

Some of the sick turkeys and random turkeys from the other two groups were sent to the School of Veterinary Medicine of Texas Agricultural and Mechanical College, College Station, Texas, for examination.

The pathologic examination of the sick turkeys revealed evidence of ornithosis, and the virus was isolated from the birds of the older group but not from the other two groups. The carcasses which had been sent to the Texas Department of Public Health Laboratories were also found to contain viable psittacosis virus.

It was concluded from these studies that turkeys were the source of the human infection in the Houston wholesale produce processing plants. None of the turkeys sent to the Dallas plant were studied, and no instance of infection among the employees was reported.

All of the birds remaining at the farm were subsequently treated with tetracycline and ultimately cleared of the infection and shipped to market. It is of some interest that the turkeys were purchased from a hatchery at Malone, Texas, a town which has been the site of a previous outbreak of psittacosis among poultry-house workers.

Summary

An outbreak of ornithosis occurring among employees of a poultry processing plant was investigated. Twenty of forty-one employees had a symptomatic illness,

and thirteen of the forty-one had a rising complement-fixing antibody titer. The source of the infection was traced to a flock of turkeys processed in the plant one week prior to the first illness. Psittacosis virus was isolated from frozen, "dressed" turkeys and from live turkeys remaining at the farm. The attack rate among employees was correlated with the exposure to dust and feathers.

The history of the epidemiology of psittacosis is reviewed.

The following persons made this study possible: (1) Dr. J. V. Irons, D.Sc., Director of the Texas State Department of Health Laboratories; (2) members of the Harris County and Houston City Health Department Laboratory; (3) R. A. Silverman, M.D., Plant Physician; (4) J. P. Delaplane, D.V.M., and Don Davis, D.V.M., of the School of Veterinary Medicine, Texas Agricultural and Mechanical College; (5) R. S. Martin, D.V.M., Veterinary Division of Houston City Health Department.

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Dyschondroplasia and Hemangiomata (Maffucci's Syndrome). II

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In 1955, I described two patients with Maffucci's syndrome and an infant with lesions suggesting the same diagnosis. I surveyed most of the cases reported up to that time since the classic modern description of the syndrome in 1942 by Carleton, Elkinton, Greenfield, and Robb-Smith. My purpose now is to record another case, report current observations on the two surviving patients described in 1955, discuss additional reports, some of which I overlooked in my earlier paper, and consider briefly some related syndromes. This rare disease is evoking much interest among internists, orthopedic surgeons and dermatologists.

It would appear that Maffucci's original paper has been inaccessible to most contemporary writers on this syndrome, and even his name is spelled with casual indifference. Recently I have obtained from what was the old Surgeon-General's Library a photostat of the original report by Angelo Maffucci from the Institute of Pathological Anatomy at the University of Naples. Maffucci's description of the first patient with this disorder deals with a forty-year-old woman who had four healthy sons. The photographs, the histological sections, and the details of the case with the extensive pathologic report from the autopsy have hardly been improved upon in all the subsequent reports. As has been true in so many other patients with this syndrome, some of the lesions had undergone sarcomatous changes. This report thoroughly deserves to be established as a minor medical classic.

The syndrome is an inborn error of tissue fabrication, a dysplastic mesodermal anomaly in which angioma, phlebectasia, vascular hamartoma, and dyschondroplasia occur in various combinations, separated in different parts of the body or closely intermingled. Often the lesions are asymmetrical but rarely unilateral. Neither the vascular nor the cartilaginous disorder is dependent on the other, but by definition both must occur in the same patient but not necessarily in the same location. The dyschondroplasia does not differ from that found in Ollier's disease.

Report of a Case

The patient was a 56-year-old bachelor, a successful broker who came to see me because he had heard of my interest in Maffucci's syndrome. He was a member of a perfectly normal family. His father died in his late 60's of cancer, and his mother died of heart trouble at the age of 70. They were not consanguineous. No member of the family

Fig. 1.—The left hand, illustrating the irregular bulbous veins and the dyschondroplastic abnormalities of the fingers.

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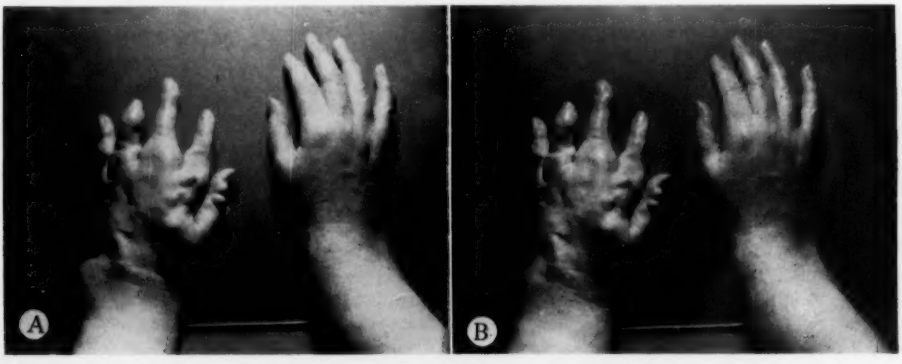
Fig. 2.—Infrared photograph of the arms, revealing gross deformities of bones and the prominent veins. The middle finger of the left hand was red and shiny.

had any deformity or lesion similar to his. Two older sisters have been completely normal as far as their skeletal, muscular, and cardiovascular systems are concerned. No member of a numerous tribe of cousins, aunts, or uncles has or has had a similar disease.

He first noticed his trouble early in life and does not remember a time when he was free of it. He was forced to use crutches from the age of 6. He managed to get along, though he broke his leg many times. He continued to have difficulty but earned enough money to put himself through college. At the age of 32, having fractured his left leg nine different times, he had a midthigh amputation at the University of Rochester Hospital. On a recent visit there he found that in addition to the dyschondroplasia, a sarcoma had been detected at the end of one of the deformed toes of the amputated leg, though he had not known it at the time. He has led an active life as a broker, getting along pretty well on his prosthesis despite some instability and a few falls. His general health has been fairly good. He has never had any more operations, though recently several physicians have recommended further surgery.

Examination revealed a man whose height was 5 ft. 5 in.; weight, 178 lb.; temperature, 98 F; pulse, 80; respirations, 16, and blood pressure 140/64 mm. Hg. The thyroid was diffusely enlarged, firm, and without bruit. It formed an easily seen goiter. There were no clinical signs of thyroid dysfunction. There was conspicuous deformity of his right arm, with foreshortening of the upper part of the arm and the forearm as well as great deformity in the hand, with characteristic findings revealed in the photographs (Figs. 1-3). There was an extensive angiomatous alteration of the hand. On his left wrist was an angioma nearly as big as a golf ball. After it was emptied by compression, blood slowly refilled it. In both palms were rubbery-looking dark venous blebs which were slowly erectile after compression. They had the consistency of thin rubber nipples. He had an easily reducible right inguinal hernia and definite deformity of the right arm, with considerable shortening of the ulna. Protrusion of the proximal portion of the radius for an inch or more interfered with complete bending of the elbow. There was some scoliosis. Although the heart and lungs were not abnormal on physical examination, an x-ray of the chest revealed enlarged hilar nodes and an infiltrate with fuzzy margins in the right upper lobe. There was a single scrotal angioma, the faintest early sign

Fig. 3.—Comparison of the hands. *A*, the large bulbous vein over the end of the ulna is prominent. *B*, it has been compressed and is refilling slowly.



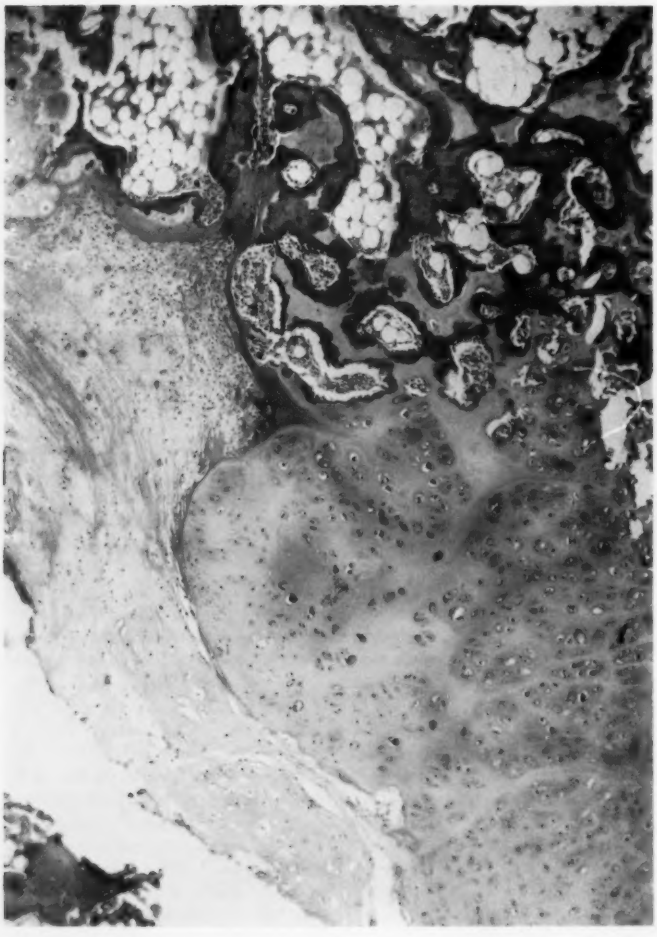


Fig. 4. — Dyschondroplasia. An osteochondroma of the clavicle from Case 1.[1] The usual regular columns of cartilage cells and the ordered transformation into bone are lost in a distorted and confused tangle of elements of cartilage and bone.

of the Fordyce lesion. There had been some recent extension of the deformity in the right hand and wrist, with redness, swelling, slight pain, and shininess of the tense skin overlying the deformed bone and cartilage. He was seen in consultation with Dr. Ponseti in our Orthopedic Department. We agreed that in all probability he had an osteosarcoma. He was unwilling to have the local lesion removed or the hand amputated. When heard from almost a year later, toward the end of 1957, his condition was unchanged and his health seemed to be about as usual.

Progress Note on Case 2 of the 1955 Paper [1]

The patient is now 20 years old. There has been no major change in the clinical condition. Growth has slowed. The deformities of cartilage and bone are progressing very little if at all. In walking, use of the warped hands, and her social adjustment she has continued in a way which is a pleasing surprise to the physicians who follow her course. No new form of therapy has been suggested.

Progress Note on Case 3 of the 1955 Paper [1]

This boy is now 4 years old. His deformed foot and leg are growing slightly faster than their normal mates, though no further surgical repair of the foot has been found. It is possible that this boy has the combined congenital dysplastic angiopathy of skin and underlying tissue. Such disorders have been called the Klippel-Trenauny or the Sturge-Weber-Kalischer syndrome, depending on whether a limb or the head and brain are involved.

This possibility was suggested to me by Dr. Vollmar, of Heidelburg, Germany.

Review of Additional Cases

In my earlier paper on Maffucci's syndrome, I continued the numbering system for case reports begun by Carleton and her colleagues. I will simply add the overlooked cases and continue the series, leaving in the doubtful one of my first cases. Surely there are other reported cases which I have missed, since there is small hope of a complete collection, even of so rare a disease.

31. I overlooked Coppen's report, of 1947, about a 38-year-old painter who had injured the fingers of the left hand when he was 8 years old. Soon afterward, tumors developed on the fingers. They turned out to be benign chondromas. Some of the tumors were elevated, but none was painful. Subsequently, another accident was followed by an aggravation of the process and an increase in size of the tumors. Circulation of the left hand was much increased, as demonstrated by oscillometry. An x-ray revealed alteration of the bony trabeculae of the epiphyses, with interruption of the peritosteum at various places. There were a number of subcutaneous angiomas.

32. Cabitza, in 1951, described a young woman of 25 who, at the age of 7, had noticed the development of tumors of the left hand. Later on the right hand became involved. The lesion was characteristic of dyschondroplasia. Chondromatous and angiomatous nodules were found in the umbilicus, the histologic section revealing cavernous fibroangiomas. One of the fingers had to be removed, and this permitted the histological verification that the tissue was myxochondromatous. Cabitza discussed at some length the differential diagnosis between Maffucci's syndrome, Ollier's disease, and the Klippel-Trenaunay syndrome.

33. Fevre and Alptekin, in 1954, recorded another case with fibroangiomas and diffuse chondromatosis. I have not been able to consult the original, which was called to my attention by Aimes and Franchebois and Tapié.

34. In 1955, Aimes and Franchebois related the history of a 44-year-old woman with a negative family history. She had been troubled since the age of 14 by slowly progressing deformities of the legs, feet, arms, and hands, worse on the right side, with nodular vascular lesions of the hands, and vitiligo. Biopsy confirmed the opinion that the erectile lesion of the hand was a cavernous angioma. Ulcerations and chronic infection ultimately led to amputation of the leg. Study of the tissue revealed dyschondroplasia, phlebectasia, and phleboliths. Aimes and Franchebois discussed the various aspects of dyschondroplasia, the pure form called Ollier's disease; dyschondroplasia with vascular anomalies, the Maffucci's syndrome; dyschondroplasia and cutaneous pigment anomalies; the combination of cutaneous angiomas and birthmarks with underlying change in the bone, which has been called the Trelat-Monad syndrome of angioma with unilateral hypertrophy of bone; the Klippel-Trenaunay syndrome of cutaneous angiomas and varices with unilateral hypertrophy of bone, or Parkes-Weber's hemangiomatous hemihypertrophy.

Maurice Tapié wrote his thesis for the Faculty of Medicine at the University of Montpellier in 1954, using the patient of Dr. Aimes as a subject and reviewing the majority of the reports published up to that time. He called attention to the observations of Cruveilhier and Hansen, who saw examples of the combined lesions before Maffucci but scarcely elaborated upon them.

35. In 1835, Cruveilhier, in his "Atlas of Pathologic Anatomy," protrayed an amputated right hand which bore multiple angiomas with phlebectasia and dyschondroplasia of the digits. Nothing further is known about the specimen or the person.

36. In 1863, Hansen described a man of 60 years whose right shoulder was the site of a chondrosarcoma which appeared after an injury. At autopsy he had a

cavernous angioma and phlebectasia of the right hand.

Gould and Pyle, in their chamber of horrors compilation of human freaks and grotesqueries, have a picture of a man with Maffucci's syndrome. It is the case of Steudel (see photograph in Reference 11).

37. Marcozzi and Messinetti, in 1956, described a 30-year-old woman with Maffucci's syndrome. At the age of 5, changes in the fingers of the right hand began, together with a tumefaction of part of the subcutaneous tissue of the thorax and abdominal walls. Ultimately many bones throughout the body became affected. Extensive x-ray studies revealed various deformities of shoulder, scapula, and bones of the skeleton generally. They give an extensive review of the literature and a detailed discussion of the problem.

38. In 1956, Sariñana, Figueroa, and Trujillo recorded clinical and laboratory studies of two new patients with Maffucci's syndrome. Their first patient, an 8-year-old boy, had a fearful deformity of the right arm, with nodular bulbous cauliflower-like lesions, while the left arm was relatively free from lesions. X-ray films of the chest disclosed a diffuse consolidation of the upper and middle parts of the right hemithorax, while the base was clear. The nature of this consolidation was not disclosed. Other films revealed the characteristic disorganization of bone and cartilage, phlebectasia, phleboliths, and angiomas with widespread anomalous vascular connections.

39. The second patient, a boy 11 years old, for years had had an increasing deformity of the left hand and arm. He had dislocations and fractures of the arm. The hand was grossly deformed. There were nodular angiomas and large varicose veins on the hand and forearm. X-ray studies demonstrated deforming dyschondroplasia of several bones of the hand and forearm, with evidence of healed fractures. Their paper is illustrated with excellent photographs.

40. Cameron and McMillan, in 1956, reported another patient with Maffucci's syndrome, a 12-year-old boy who had a single chondroma but angiomas of skeletal muscle, subcutaneous tissue, and periarticular tissue, with a prominent tumor-like infiltration of the semiteninosus muscle and short head of the biceps femoris of the right leg. Apart from the many small angiomas scattered throughout the muscle, the pathologic changes resembled those of the late stages of pseudohypertrophic muscular dystrophy. Cameron and McMillan suspected that the angiomas, acting as arteriovenous shunts, starved the muscle of oxygen and led to muscle atrophy with fatty replacement.

Comment

Sabanas and Ghormley reported a 37-year-old woman with hemangioma of the knee joint complicated by synovial chondromatosis, but there is no close connection with Maffucci's syndrome. Stauffer, Arbuckle, and Aegerter have described a case of polyostotic fibrous dysplasia and congenital arteriovenous aneurysms, but a study of their report suggests that their case was far different from Maffucci's complex. In fact, there is little danger of confusing the two except on the most superficial inspection. Murray's case of melorheostosis and congenital arteriovenous aneurysms is another disorder with bone lesions and a vascular component, but here too there is no likelihood of confusion. These and other relations of melorheostosis have been discussed in a detailed and searching review of this peculiar sclerosing osteopathy by McGuinness, Watson, Lindsell, and Inglis. A suggestion of some possible relationship of neurofibromatosis and such a disorder as Maffucci's syndrome might be inferred from the stimulating studies and speculations of Inglis, but at present I see little overlapping and only rarely any chance of confusing these usually discrete clinical disorders.

There is now a larger number of cases for analysis, although no new insights have been gained. Of 39 with adequate data, 15 were girls or women and 24 were boys or men. The youngest was an infant, and the oldest was 60, so the disease may be recognized early in life. Despite the risk of neoplasm, Maffucci's syndrome does not necessarily cause an early death.

Maffucci's syndrome, the strange mixture of dyschondroplasias and vascular anomalies, is an inborn error of structure, a developmental dysplasia, congenital but not inherited. The anomalies of cartilage and blood vessels may be separate or jumbled together, but there is no necessary physical connection. Presumably the single warped gene governs two tissue elements, cartilage and blood vessels. The lesions are likely to be much more extensive on one side than the other, but they are not unilateral except early in the disease.

The disease may be identified early in life from the deformities of cartilage and bone which favor the occurrence of fractures and the warping and bending of the skeleton. Malignant tumors, especially sarcomas, are unusually common. In several patients, the one under consideration here, Case 1 of the 1955 report, and some of those figured by Carleton and her colleagues, enlargement of the thyroid was noted. No signs of myxedema or thyrotoxicosis have been reported, so we suspect that hamartomas of different kinds of tissue may be responsible. This may be the same sort of thing which has been described in the superficial tissues over the abdomen or chest but not investigated by histologic study.

The nature of the pulmonary infiltrates in our patient and one of those reported by Sariñana, Figueroa, and Trujillo is uncertain but possibly may be pulmonary metastases from sarcoma or other neoplasm.

Many of the larger almost cirsoid clusters of veins and some of the smaller ones have phleboliths which may be identified by x-ray, at operation, or at autopsy.

Summary and Conclusions

Maffucci's syndrome, the occurrence in one person of dyschondroplasia, vascular anomolies, and hamartomas, has now been recorded in at least 41 instances, 4 having been observed in a single hospital. It produces serious deformities but is compatible with an active and useful life. More men than women have been reported. It may be recognized in early childhood and continue into late years, though there is a serious risk of neoplasm, particularly in those of the sarcoma group. Its cause is a mystery. Beyond the surgical correction of deformed bones and amputation, no treatment is known.

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"Infarctoid Cardiopathy" Produced by Hydrocortisone and Monobasic Sodium Phosphate

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It has long been known that many actions of hormones are not direct but are due to the creation of favorable conditions for the actions of nonhormonal agents.[1] In our institute this phenomenon of "conditioning" by hormones of the sensitivity to nonendocrine stimuli has been studied, particularly in relation to the actions of electrolytes. It was found, for example, that the production of nephrosclerosis, myocarditis, and periarteritis nodosa by deoxycorticosterone does not depend upon the direct effects of the hormone but upon its ability to sensitize tissues to dietary sodium chloride.[2,3] Apparently, it is through an essentially similar mechanism that deoxycorticosterone produces favorable conditions for the production of nephrocalcinosis, by the concurrent administration of, in themselves, inactive doses of phosphate.[4]

A particularly striking instance of the selective conditioning of cardiac tissue for the toxic actions of dietary sodium phosphates (NaH_2PO_4 and Na_2HPO_4) has recently come to our attention. Rats treated concurrently with certain highly active corticoids (e. g., the 9α-halogenated steroids) and NaH_2PO_4 invariably succumb with the clinical manifestations of acute cardiac death. In their myocardium, autopsy regularly reveals large, yellowish, infarct-like, necrotic patches. Histologically, these lesions also resemble the true spontaneous cardiac infarcts of man; like the latter, they consist of large sharply delimited foci in which the myocytes first disintegrate and are then invaded by histiocytes and polymorphonuclear cells. This similarity is further emphasized by the fact that sudden exposure to stress can precipitate the development of massive cardiac necroses in rats pretreated with subthreshold doses of NaH_2PO_4 plus corticoids. On the other hand, the experimental lesion essentially differs from ordinary infarcts in that histologically demonstrable vascular occlusions do not occur in the former. To emphasize both their resemblance to, and distinctness from, true cardiac infarcts, these lesions have been referred to as an "infarctoid cardiopathy."[5-7]

The demonstration that the myocardium can be selectively conditioned to inorganic salts raised the hope that the newly discovered interaction between sodium phosphates and steroids might help to elucidate certain basic problems of cardiac physiology, as well as the puzzling but not uncommon cardiac infarcts which occur without evidence of acute coronary occlusion in man.[8-14] However, we felt that as a preliminary to clinical investigations along these lines we had to establish whether the principal naturally secreted glucocorticoid of man, hydrocortisone, can also selectively condition the heart to the actions of orally administered sodium phosphate and whether the "infarctoid cardiopathy" can be experimentally induced in primates. The observations to be reported in this communication will show that both these questions can be answered in the affirmative.

Materials and Methods

Eighteen female rhesus (Macaca mulatta) monkeys, with a mean initial body weight of 2520 gm. (range, 2250-3150 gm.) were subdivided into seven groups, as indicated in the Table. Throughout the experiments the animals were given a mixed diet,

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Cardiac Necroses and Mortality Induced by Corticoids Plus NaH_2PO_4 in the Monkey

Group	Monkeys, No.	Treatment	Cardiac Necroses: Incidence, %	Cardiac Necroses: Grade (Scale, 1-3)	Mortality, %
I	3	None	0	0	0
II	3	NaH_2PO_4	0	0	66
III	2	Hydrocortisone	0	0	0
IV	2	Hydrocortisone + restraint	100	1	0
V	3	Hydrocortisone + NaH_2PO_4	100	1	66
VI	3	Hydrocortisone + NaH_2PO_4 + restraint	100	3	66
VII	2	2α-methyl-9α-chlorohydrocortisone + NaH_2PO_4	100	2	100

consisting of carrots, apples, lettuce, and bread. In order to produce a *neuromuscular stress situation*, the monkeys (see below) were strapped in the prone position to a wooden board with adhesive tape (placed around ankles and wrists) for a period of 18 hours on the 12th day of the experiment.

Hydrocortisone was injected in the form of a microcrystal suspension of its acetate, at the daily dose of 100 mg. in 4 ml. of water, subcutaneously; 2α-methyl-9α-chlorohydrocortisone was also administered in the form of microcrystals of its acetate, but at the daily dose of 1 mg. in 1 ml. during the first seven days and 3 mg. in 1 ml. during the rest of the experiment. Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$) was always given twice daily, by stomach tube, but the initial dose of 5 ml. was gradually raised to 10 ml. (third day), 20 ml. (fifth day), 40 ml. (seventh day) and, eventually, 80 ml. (ninth day). This last dose level was given until the termination of the experiment on the 13th day, when all the surviving monkeys were killed with chloroform.

Specimens of all the hearts, kidneys, and pancreases were fixed in neutral formalin for subsequent staining with hematoxylin and phloxine (to show general structure), and with von Kossa's silver nitrate technique (for the histochemical demonstration of calcium). The pancreas was examined, because in earlier experiments we had noted that in rabbits infarctoid cardiopathy produced by combined treatment with steroids and phosphates is occasionally accompanied by acute pancreatitis. Von Kossa's technique was employed because this type of treatment regularly produces some degree of nephrocalcinosis in rats.

Results

Our results are summarized in the Table, which lists the incidence (per cent positive) and the severity (graded in terms of an arbitrary scale of 1 to 3) of the cardiac necroses, as well as the mortality rate.

The large amount of orally administered NaH_2PO_4 was not well tolerated by the rhesus monkeys; they developed an intense bloody diarrhea, and two out of the three animals treated with phosphate alone (Group II) died on the 12th day. Curiously, the diarrhea was much less pronounced and the stools were virtually free of blood in the monkeys which received, in addition to the phosphate, hydrocortisone or 2α-methyl-9α-chlorohydrocortisone and which developed severe "infarctoid cardiopathy"; hence, the mortality in these last two groups is most probably the direct result of the cardiac damage.

Despite careful examination of many sections taken at about 0.5 cm. intervals throughout the myocardium, no histologic lesions could be demonstrated in any of the untreated controls (Group I) or in the monkeys given NaH_2PO_4 alone (Group II) or hydrocortisone alone (Group III). On the other hand, large, yellowish, infarct-like patches were evident on naked-eye inspection in the hearts of several monkeys (two in Group V, all in Group VI, and one in Group VII), and histologic study revealed the presence of myocardial necroses in all of the monkeys in Groups IV-VII. These lesions consisted of more or less sharply delimited foci, in which the myocardial fibers became homogeneous and were gradually invaded by histiocytes and polymorphonuclear leukocytes. Infiltration with the latter cells was most prominent at the borderlines between necrotic and healthy myocardial tissue. However, there was no evidence of coronary artery disease in any of our animals (Figs. 1-4). In addition, more or less extensive subendocardial

Fig. 1.—Macroscopic aspect of the heart in one of the monkeys exposed to the neuromuscular stress of restraint after pretreatment with NaH_2PO_4 plus hydrocortisone. Note the light necrotic area just below the dotted line.

Fig. 3.—Minute necrotic patch in the heart shown in Figure 1 as it appears under high magnification. In this recent lesion there is no inflammatory reaction. Hematoxylin and phloxine; × 400.

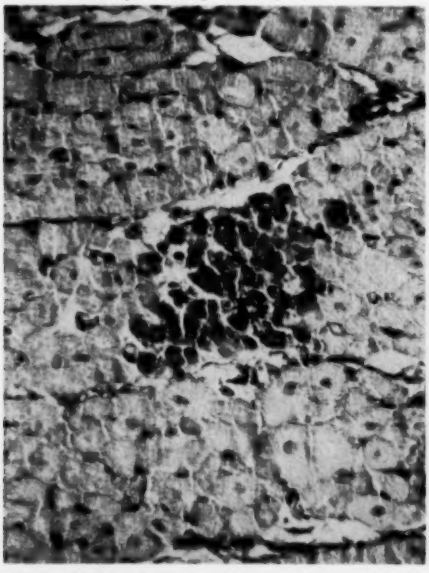
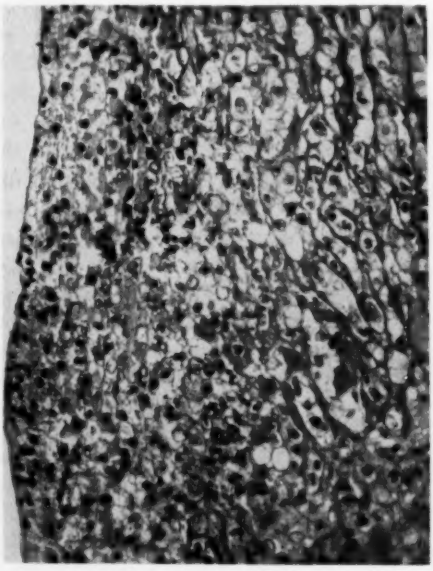


Fig. 2.—Several necrotic (dark) patches in the subendocardial layer and in a papillary muscle of the heart shown in Figure 1. Hematoxylin and phloxine; × 35.

Fig. 4.—Somewhat older subendocardial necrotic patch in the heart of a monkey treated with NaH_2PO_4 plus 2α-methyl-9α-chlorohydrocortisone without exposure to stress. Here, the muscle fibers have been largely absorbed and replaced by inflammatory cells and edema. Hematoxylin and phloxine; × 400.



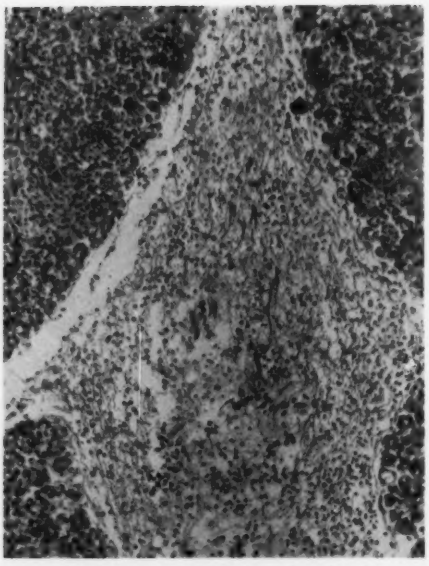


Fig. 5.—Edema and inflammation in the pancreas of a monkey exposed to the neuromuscular stress of restraint after pretreatment with NaH_2PO_4 plus 2α-methyl-9α-chlorohydrocortisone. Hematoxylin and phloxine; × 100.

hemorrhages were noted in all of the monkeys that exhibited myocardial necroses.

Apart from the cardiac lesions, no manifest morphologic changes could be detected, except for a rather intense purulent pancreatitis (Fig. 5) in two of the monkeys in Group VI and occasional calcification of convoluted tubules in the kidneys of all monkeys in Groups V-VII.

Comment

Since none of the animals treated with either NaH_2PO_4 or hydrocortisone only showed the slightest evidence of cardiac necrosis, it appears that in monkeys conditioned by large doses of hydrocortisone severe acute myocardial necroses can be elicited by restraint (Group IV), NaH_2PO_4 (Group V), and restraint plus NaH_2PO_4 in particular (Group VI). This confirms earlier observations performed under essentially similar conditions but on a much larger group of rats.[5] It is also clear that 2α-methyl-9α-chlorohydrocortisone (Group VII) is considerably more active than hydrocortisone as a conditioning agent for the cardiotoxic action of NaH_2PO_4.

The most interesting question raised by these observations is the possibility of a relationship between this experimental "infarctoid cardiopathy" and certain cardiac derangements that occur in man. Previously, there had been no reason to suspect that glucocorticoids could cause infarct-like myocardial lesions; hence, the development of the latter, in patients treated with corticotropin (ACTH) or glucocorticoids, would have been considered to be purely coincidental. Besides, as all our earlier experiments on the rat and the present observations on monkeys indicate, even enormous doses of these hormones do not, in themselves, elicit myocardial necroses but merely condition for their production by NaH_2PO_4 or stress, for example. Nevertheless, the literature does contain a few instances of cardiac infarcts that apparently occurred as a result of corticotropin or glucocorticoid treatment.[15-19]

In all our monkeys, the myocardial necroses occurred in the absence of any demonstrable vascular occlusion. This fact deserves special comment. In our introduction we cited the literature on typical cardiac infarcts that occurred in patients in whom it was impossible to demonstrate any acute vascular obstruction. Apparently, the production of a myocardial necrosis—especially in conditions of acute stress—depends not only upon the blood supply, but also, and to a very great degree, upon the metabolic requirements of the myocardium: its need for oxygen, nutrients, and the removal of toxic waste products. The humoral derangement produced by glucocorticoids (especially when these are given in combination with NaH_2PO_4) may simply condition the myocardium for the production of necrosis by any stimulus that increases the metabolic demands of the heart.

It must also be kept in mind that all our experiments were performed on healthy young animals with normal cardiac vessels, while spontaneous infarcts tend to occur

with the greatest frequency in middle-aged or older men. In these men, even a moderate degree of coronary sclerosis may well act as a predisposing factor for metabolic changes similar to those that are induced by combined treatment with phosphates and steroids in animals. It was thought that, in order to elucidate this problem, it would be useful first to produce a moderate amount of coronary sclerosis (for instance, by treatment with dihydrotachysterol) and then to determine whether such an "artificial aging" of the arterial system can sensitize the heart to the necrotizing effect of subsequent treatment with phosphate and steroid. Overdosage with vitamin D derivatives, such as dihydrotachysterol, tends to cause a rather diffuse sclerosis of the entire coronary system; consequently, if our hypothesis were correct, it could be expected that after such treatment, the cardiac muscle would become extraordinarily sensitive to the necrotizing effect of subsequently administered phosphate and glucocorticoid. This hypothesis has recently been verified by experiments in the rat,[20] although no such observations have been made as yet in primates.

Another spontaneous disease of man which resembles the "infarctoid cardiopathy," although it has never been suspected of having any relationship to true cardiac infarcts, is the so-called "acute isolated myocarditis of Fiedler." Here—as in the experimental "infarctoid cardiopathy"—the essential lesion is a patchy myocardial necrosis subsequently infiltrated by histiocytes and polymorphonuclear leukocytes. The focus is not due to organic lesions in the coronary vessels. It has been called "isolated" because it is usually unaccompanied by manifest organ changes outside the heart.[21] This disease appears to be closely related to the "nonspecific myocarditis in infants," [22] the "acute miliary infarction," [23] "subendocardial necrosis," [24] "endomyocardial necrosis (or fibrosis)," [25,26] certain types of "toxic myocardiopathy," [27] "myocarditis perniciosa," [28] and many other obscure cardiopathies in which myocardial necrosis occurs in the absence of acute vascular obstruction and is followed by inflammation (e. g. the "necrotizing myocarditis" usually ascribed to microbial toxins).

Finally, we should like to call attention to the fact that—at least in the rat—the production of "infarctoid cardiopathy" by combined treatment with glucocorticoids and sodium phosphate can be completely prevented by the oral administration of magnesium chloride or potassium chloride.[7]

It remains to be shown whether the various experimental and clinical conditions which we have just discussed are in fact due to some closely related metabolic derangement within the myocardium and whether the therapeutic measures that proved effective in the experimental "infarctoid cardiopathy" could serve as a basis for the development of new therapeutic measures applicable to spontaneous cardiac diseases of man. However, it is well established, now, that acute myocardial necrosis (followed by inflammatory changes within the affected foci) can be produced at will in various experimental animals, among them, the primate, by combined treatment with NaH_2PO_4 and various corticoids, including the principal natural glucocorticoid of man. From our earlier experiments on the rat, it is equally clear that such experimental myocardiopathies can be prevented by magnesium and potassium salts.

Summary

Experiments on a primate (Macaca mulatta) indicate that treatment with large doses of natural glucocorticoid (hydrocortisone) can so condition the cardiac muscle that it responds to severe neuromuscular stress, with the development of extensive acute myocardial necroses.

Combined treatment with hydrocortisone and NaH_2PO_4 produces such infarct-like myocardial changes, even in animals not exposed to stress.

In monkeys pretreated with hydrocortisone plus NaH_2PO_4, subsequent exposure to a neuromuscular stress produces particularly pronounced and extensive myocardial necroses.

The relationship between this experimental "infarctoid cardiopathy" and various spontaneous diseases of man has been briefly discussed, especially in view of the fact that earlier observation (on rats) showed that the experimental "infarctoid cardiopathy" can be prevented by prophylactic treatment with magnesium or potassium salts.

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Studies on "Prothrombin Derivatives" in Vitamin K Deficiency

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Certain of the blood-clotting factors have a number of properties in common. These properties include affinity for the insoluble salts of heavy metals (i. e., barium sulfate), relative heat lability and storage stability, and lack of utilization during the course of clotting. The last-named property, whereby serum contains these factors in undiminished titer, has led some investigators to use the term "serum factors." The presently accepted "serum factors" are Factor VII, plasma thromboplastin component (PTC), and Stuart factor.[1]

Except for its utilization during clotting, prothrombin shares the above-mentioned properties of the "serum factors." These similarities have suggested the "serum factors" are derivatives of or share a common synthetic pathway with prothrombin. Evidence for this view has been provided by the finding that all are depressed following administration of bishydroxycoumarin (Dicumarol) and related drugs,[2-5] suggesting that vitamin K is necessary for their synthesis. Moreover, it has been possible to demonstrate in vitro interconversion of prothrombin and Factor VII.[6,7]

The present study concerns a patient who had vitamin K deficiency on the basis of intestinal malabsorption. This condition provided a unique opportunity to study the dependence of prothrombin and the "serum factors" on vitamin K, in the absence of medication.

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Subject and Methods

The patient was a 48-year-old Puerto Rican woman who had been in the United States since 1946. In 1953, "pernicious anemia" had been diagnosed at another hospital, and in 1955, a diagnosis of sarcoidosis was established by bronchoscopic biopsy and a positive Kveim test. Pulmonary tuberculosis was suspected in 1956, but repeated sputum examination failed to reveal acid-fast bacteria. Nevertheless, the patient received a course of therapy with streptomycin and isoniazid. Early in 1957 the patient began to lose weight, which amounted to 40 lb. in a period of about seven months. This was accompanied by progressive pallor and intermittent diarrhea. Pertinent findings on physical examination included only a moderately smooth tongue and hepatomegaly. The laboratory findings, summarized in the Table, show evidence of multiple deficiencies and intestinal malabsorption. After the Schilling test there was marked symptomatic improvement followed by virtually complete hematological remission. The provisional diagnosis was tropical sprue.

Prothrombin.—The prothrombin time was determined by the methods of Quick and Ware and Stragnell.[8] In addition, a "true" prothrombin assay was performed by a modification of the method described by Owren and Aas.[9] In this modification an excess of other clotting factors was provided by a reagent consisting of barium sulfate-adsorbed beef plasma (Ware and Stragnell), 2 vol., to 1 vol. of normal human serum. The reagent was prepared freshly for each series of tests, and test specimens were diluted to 5% in isotonic saline.

Factor VII.—Factor VII was estimated as follows: Plasma from a patient with congenital Factor VII deficiency* was diluted to 10% in saline. Four volumes of this diluted Factor VII-deficient plasma was added to one volume of test plasma also diluted to 10%. A Ware and Stragnell prothrombin time was performed on the mixture in the usual fashion.

Stuart Factor.—This factor was measured as follows: One volume of test plasma was added to nine volumes of plasma deficient in Stuart factor.†

* Provided by Dr. Robert Rosenthal.

† Provided by Drs. J. B. Graham and C. Hougie.

Laboratory Data for Patient

Test	Result	
Hematocrit	23%	
Red blood cell count	2,300,000/cu. mm.	
Hemoglobin	7.5 gm/100 cc.	
Reticulocytes	1%	
Bone marrow	Megaloblastic; abundant hemosiderin with Prussian blue stain	
Schilling test	Excretion of $Co^{60}B_{12}$: Without intrinsic factor	0.35%
	With intrinsic factor	0.67%
Leukocyte count	8,000/cu. mm.; normal differential count	
Platelet count (Phase)	155,000/cu. mm.	
Glucose tolerance test	Oral	Intravenous
Blood sugar, mg/100 cc.		
Fasting	89	76
½ hr.	88	214
1 hr.	98	112
2 hr.	95	79
3 hr.	87	103
Blood urea nitrogen	5.1 mg/100 cc.	
Serum calcium	9.2 mg/100 cc.	
Serum phosphorus	4.1 mg/100 cc.	
Serum protein	Albumin 3.5%; globulin 2.8%	
Serum bilirubin	1.2 mg/100 cc.	
Cephalin flocculation test	1+	
Thymol turbidity	3 units	
Serum transaminase	51 units	
Prothrombin time		
Quick	22.6 sec.	
Ware & Stragnell	38.6 sec.	
Plasma fibrinogen	360 mg/100 cc.	
Labile factor (Quick)	100%	
Chest x-ray	No evidence of active pulmonary lesions	
X-ray examination of gastrointestinal tract	Sliding hiatus hernia, deformed duodenal bulb, minimal motor disfunction of small bowel	

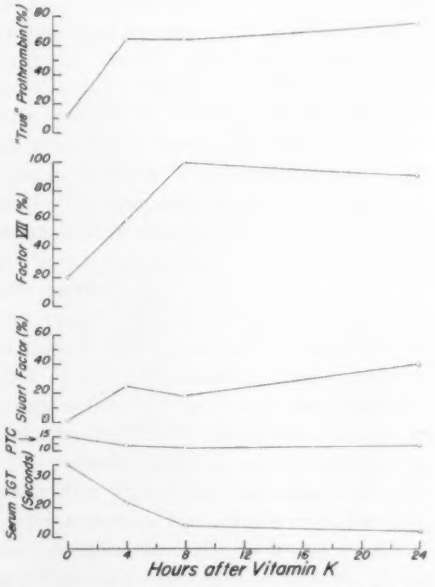
A Quick prothrombin time was performed on the mixture.

Plasma Thromboplastin Component.—PTC was assayed in a modified thromboplastin-generation test. Serum from a patient with established and severe PTC deficiency was diluted to 20% with isotonic saline. To this reagent an equal volume of test serum diluted to 1% was added. The mixture was used as serum reagent in the thromboplastin-generation test with bovine plasma reagent and crude human brain "cephalin." An additional check on PTC activity was accomplished by the prothrombin-consumption technique, in which test plasma was added to PTC-deficient whole blood at a final concentration of 1%. Serum prothrombin was measured one hour after clotting by the technique of Ware and Stragnell.

Thromboplastin-Generation Test.—This test was performed by our modification[11] of the original method described by Biggs and Douglas.[12]

Results

The Figure shows the initial pattern of the patient's "prothrombin derivatives" and their response to the intravenous administration of 50 mg. of phytonadione (vita-



Response of prothrombin and the "serum factors" to vitamin K.

min K_1). Before treatment, Stuart factor was most severely depleted and there was moderate reduction of prothrombin and Factor VII as well. PTC was slightly if at all affected, as shown by the thromboplastin-generation method, and no change was demonstrable by the prothrombin-consumption technique. All depleted factors were promptly restored toward normal following injection of vitamin K. Of these, Stuart factor showed the most sluggish response.

Liver damage evidently did not play a significant role in the initial depression of the factors measured. This is shown by the prompt response to vitamin K and by the normal Factor V and fibrinogen levels.

Comment

Ample evidence has been presented in the past that prothrombin synthesis depends upon exogenous vitamin K.[13] Depression of PTC in vitamin K deficiency has been reported by Naeye,[14] Douglas,[15] and Lewis et al.[16] The data show some variation as to the relative sensitivity of prothrombin and PTC. Some investigators have found a fairly parallel depression of both factors in vitamin K deficiency[14,16] and in treatment with coumarin drugs.[5] The present findings are in accord with reports that indicate considerably greater resistance of PTC than prothrombin.[2,4] Previous studies claiming Factor VII deficiency[14,16] have failed to consider the inability to distinguish between that factor and Stuart factor by the usual methods. Our data indicate that although both Factor VII and Stuart factor are depressed in exogenous vitamin K deficiency, Stuart factor appears to be considerably more sensitive. This entire group of factors, including PTC,[4,14,16] responds promptly to vitamin K administration. The data are in general conformity with those obtained from studies with coumarin drugs. If Stuart factor is indeed identical to Factor X, as has recently been claimed,[18] the sluggish response to vitamin K reported above is similar to that following coumarin depression.[17]

Our findings are thus compatible with the concept that prothrombin and the "serum factors" are structurally and metabolically related compounds. The demonstration of vitamin K dependence in the absence of complicating drugs supplements previously obtained data. However, final proof must ultimately be derived from biochemical elucidation of the molecular structure and synthetic pathway of these compounds. Meanwhile, it is of value to know that interference with vitamin K metabolism results in a coagulation derangement considerably more complex than formerly recognized.

Summary

Coagulation studies were performed on a patient with an intestinal malabsorptive syndrome resulting in vitamin K deficiency. Initially there was a depression of prothrombin, Factor VII, and Stuart factor. Plasma thromboplastin component was not affected. Intravenous vitamin K was followed by rapid restoration of all depressed factors. The data are in conformity with the view that prothrombin and the "serum factors" are chemically and metabolically related compounds.

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Cystic Medionecrosis with Dissecting Aneurysm of Coronary Arteries

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Aortic cystic medionecrosis with extension of a dissecting aneurysm into the coronary arteries is rare, but medionecrosis and dissection of coronary arteries independent of aortic involvement is even more rare.

Since the first reported case of dissecting aneurysm of the left coronary artery with associated changes of cystic medionecrosis was described by Lovitt and Corzine,[1] in 1952, no other cases have appeared in the literature. These authors presented a case of a 39-year-old woman who died shortly after an episode of precordial pain occurring 14 days after a normal delivery. At autopsy a dissecting aneurysm was found involving the anterior descending branch of the left coronary artery, with compression and occlusion of the lumen. Histologically, changes of cystic medial degeneration were found in the coronaries, and there was minimal coronary atherosclerosis. Cystic medionecrosis of the aorta was not observed. The dissecting aneurysm evolved rapidly, for the myocardium showed no morphological evidence of acute infarction.

Uehlinger,[2] in 1947, described two cases of spontaneous dissecting aneurysm of the coronary artery but recorded no associated changes of cystic medial degeneration. His first case was that of a recently inducted 46-year-old soldier who died suddenly four days after a hike through cold and stormy weather. Autopsy revealed a dissecting aneurysm of the anterior descending branch of the left coronary artery, with compression and occlusion of the lumen. The heart was acutely dilated, and the myocardium failed to show evidence of acute infarction. The second case was that of a 45-year-old farmer who died a few days after "strenuous work" after his induction into the army. At autopsy, there was a dissecting aneurysm of the anterior branch of the left coronary artery as well as an acute myocardial infarction of the left ventricle with mural thrombosis and cerebral embolization. In neither of the cases was there significant coronary or aortic atherosclerosis, nor any medial aortic changes.

The purpose of this paper is to report four cases of cystic medionecrosis of the coronary arteries occurring independently of demonstrable lesions in the aorta. In three of these cases the coronary lesions were incidental, but in one, the medial lesions lead to a dissection within the left coronary artery and consequent fatal myocardial infarction.

Report of Case

CASE 1.—A 45-year-old white married female clerk was admitted to the hospital on Nov. 15, 1956, with a clinical diagnosis of acute myocardial infarction. On the morning of admission, after walking approximately two blocks, she developed a tightening sensation of her throat. Shortly thereafter, she experienced an episode of nausea, severe anterior chest pain, and shortness of breath. She managed to return home unassisted and after climbing three flights of stairs to her apartment felt semi-stuperous and was in a "cold sweat." She was seen by a physician within one-half hour. On physical examination she was found to be a well-developed woman in acute distress, appearing somewhat younger than her stated age. She was perspiring profusely, and her skin was cold to the touch. The heart sounds were faintly audible, and the blood pressure was 90/60 mm. Hg. The lungs were clear to percussion and auscultation, and no

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pitting edema of the lower extremities was noted. At this time the patient refused hospitalization, but with recurrence of severe chest pain one hour later, which was squeezing in character, she was again seen by a physician, who obtained an electrocardiogram and successfully urged her admission to the hospital by ambulance. The electrocardiogram taken at the patient's home showed a normal sinus rhythm with a rate of 60 beats per minute, a P-R interval of 0.16 seconds, a QRS interval of 0.06 seconds, upright P waves in all limb leads, diphasic T in Lead I; inverted T waves in Leads I and II, a Q-S and a diphasic T in aV_L, and inverted T waves in precordial leads V_4, V_5, and V_6. These findings were consistent with an early anterolateral myocardial infarction. On admission to the hospital, the patient's general condition differed little from that previously noted. Her past medical history was not relevant to the present illness. There was no previous history of hypertension, syphilis, or diabetes mellitus. Six to eight months prior to admission she was treated for chronic laryrinthitis, and five years prior to admission she underwent a vaginal hysterectomy.

Laboratory studies revealed a hemoglobin value of 15.4 gm. %. The white blood cell count was 12,000 cells per cubic millimeter, with differential cell count of 70% adult neutrophils, 4% band forms, 24% lymphocytes, and 2% monocytes. The blood sugar was 111 mg. %. The blood nonprotein nitrogen was 20 mg. %. The sedimentation rate was 10 mm. per hour. The bleeding time was 30 seconds. The clotting time was 3 minutes. The prothrombin time was 13 seconds (control, 15 seconds). The urine was essentially negative. The usual treatment for acute coronary thrombosis was instituted, including anticoagulant therapy with heparin and bishydroxycoumarin (Dicumerol). On the second hospital day an electrocardiogram showed a normal sinus rhythm with a tachycardia of 100 beats per minute, a P-R interval of 0.12 seconds; a QRS complex of 0.05 seconds; an inverted T wave with a Q wave in Leads I, aV_L, and V_2 through V_6; absent R wave in V_2 and V_3; and sagging ST segment in Leads II and III and aV_F. These changes were interpreted as consistent with a recent anterolateral myocardial infarct. On the third hospital day the precordial pain became very severe and the pulse, weak and rapid. The patient was placed in an oxygen tent, and another electrocardiogram was taken, which revealed extension of the infarction with involvement of the interventricular septum. The sinus rhythm remained normal, with an increased heart rate of 130 beats per minute. The P-R interval was 0.12 seconds; the QRS interval was 0.10 seconds; there was a high take-off, with Q waves in Leads I, aV_L, V_2, V_3, V_4, and V_5. ST segments in Leads III and aV_F were depressed. The patient rapidly developed pulmonary edema and Cheyne-Stokes respirations and despite emergency therapy died on the third hospital day.

Autopsy revealed a well-developed white woman appearing somewhat younger than the reported age of 45 years, with an estimated body weight of 57 kg. and body length of 147 cm. There was marked pulmonary congestion and edema, with slight bilateral hydrothorax of 200 ml. and acute passive congestion of abdominal viscera. The uterus was surgically absent, and the left ovary contained a recent corpus luteum. The more significant findings were limited to the heart and coronary arteries.

Coronary Arteries.—The distribution of the coronary arteries followed the commonest pattern; the right coronary artery continued as the posterior descending branch, and the left coronary artery divided into the anterior descending and the left circumflex branches. The coronary ostia were widely patent. The left main coronary artery, save for its initial 0.5 cm., appeared bulging, moderately tortuous, and purple-red. These same features were noted over the initial 2 cm. of the anterior descending and the initial 1 cm. of the left circumflex branches. Gross sections of the affected coronary arteries revealed extensive recent intramural hemorrhage, with resultant compression and virtual occlusion of the lumens. A small, slightly raised, 0.2 cm. by 0.4 cm. gray-yellow plaque represented the sole gross evidence of coronary atherosclerosis and did not appear to bear any relationship to the dissecting aneurysm.

Histologically, the coronary arteries showed a dissecting aneurysm involving the left coronary artery and initial portions of the left circumflex and anterior descending branches, with foci of cystic medial degeneration in adjacent segments. At the level of the main left coronary artery, the intramural hemorrhage split the media near the hypothetical junction of its inner two-thirds and outer one-third (Fig. 1). The bulging outer wall of the split media was extremely thinned out, with only few erythrocytes outside the external elastic membrane. A section at the level of the initial 2 cm. of the anterior descending branch of the left coronary artery failed to reveal significant numbers of extravasated erythrocytes in the adventitia or periadventitial tissue, and the dissecting hemorrhage was essentially confined to the media, with compression and near occlusion of the lumen (Fig. 2). Here, a small focus somewhat suggestive of medial cystic degeneration was present. In general, the adventitial and periadventitial tissues about the areas of dissection were infiltrated with varying numbers of histiocytes, macrophages, lymphocytes, plasma cells, occasional polymorphonuclear neutrophils, and numerous eosinophils. Clumps of altered fibrin

Fig. 1 (Case 1).—Section of left main coronary artery, with massive hemorrhage dissecting the outer media. There is marked distention of the external elastic membrane and severe compression of the lumen. Verhoeff's elastic tissue stain; approximately × 10.5.

were also present. The periadventitial capillaries exhibited swelling of the lining endothelium. The intima showed focal fibrous thickening and contained few foam cells. Sections of the left circumflex artery distal to the dissection exhibited changes typical of cystic medionecrosis (Figs. 3 and 4). With use of several histological stains (hematoxylin and eosin, Mallory's phloxine methylene blue, aniline blue, Verhoeff's elastic tissue stain, silver impregnation for reticulum, and periodic acid-Schiff stains), persistent and attenuated medial elements could be demonstrated within the areas of cystic degeneration forming a broken fibrillary network with wide interstices. These cleft-like spaces contained scanty faintly acidophilic "ground substance" which was very faintly periodic acid-Schiff-positive. In some levels, the cystic areas of degeneration involved the entire thickness of the media and the external limiting membrane was distended and slightly bulging. At the distal region of the medial dissection, the anterior descending branch of the left coronary artery showed an atheromatous plaque about the ostium of one of its small branches.

Heart.—The heart weighed 230 gm. There was moderately abundant epicardial fat and an estimated 20 ml. of clear straw-colored pericardial fluid. Sections through the myocardium revealed extensive deep-red mottling of the anterolateral wall and anterior half of the interventricular septum. This mottling extended from the lower margin of the upper third of the left ventricle to the apex.

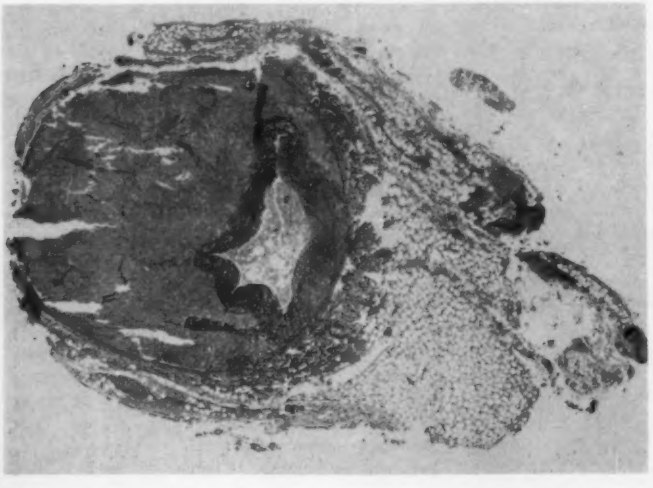
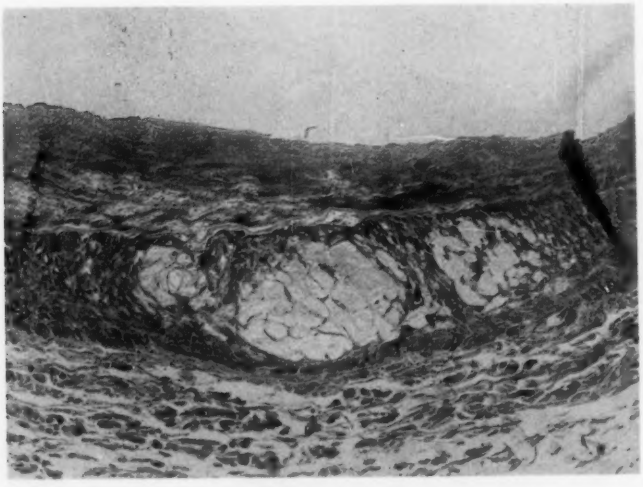
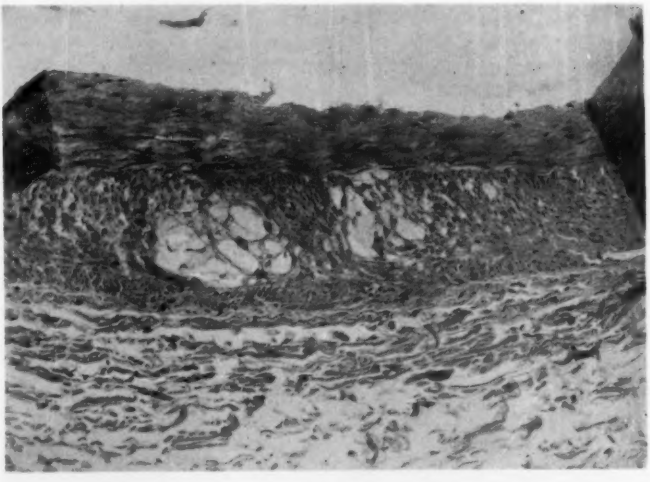


Fig. 2 (Case 1).—Section of anterior descending branch of left coronary artery, showing a dissecting aneurysm as in Figure 1. At the upper pole of the apparently intact media there is pale area suggestive of medial cystic degeneration. The right half of the intima shows slight fibrous thickening. Periodic acid-Schiff stain; × 13.





Figs. 3 and 4 (Case 1).—Sections of left circumflex branch of left coronary artery distal to dissection showing large foci of medial cystic degeneration and slight intimal fibrosis. Mallory's phloxine methylene blue stain; approximately ×125.

The semilunar and atrioventricular valves, as well as the endocardium of the atrial and ventricular chambers, including the auricular appendages, were not remarkable. The microscopic examination confirmed the existence of an acute myocardial infarct of approximately three days' duration.

Aorta.—The aorta contained minimal atherosclerotic changes in the form of slightly raised grayish-white to yellow longitudinally disposed intimal streaks or small plaques measuring less than 1 cm. in largest dimensions. These were found largely in the lower abdominal segment. In the several sections of aorta, the small intimal plaques were slightly fibrotic and contained collections of foam cells and fewer histiocytes, lymphocytes, and plasma cells. But in sections tangential to vasa vasorum there were perivascular clefts composed of basophilic ground substance and a delicate fibrillar connective tissue. Although these areas were somewhat suggestive of very early changes of idiopathic medial cystic degeneration, their constant association with the vasa vasorum made such an interpretation unlikely. Other arteries, such as the pulmonary, splenic, and renal arteries, had no significant changes.

The final anatomical diagnosis was medial cystic degeneration of coronary arteries with dissecting aneurysm of left coronary artery and initial portions of both anterior descending and left circumflex branches; acute anteroseptal myocardial infarct with involvement of anterolateral left ventricular wall, extensive; pulmonary congestion and edema

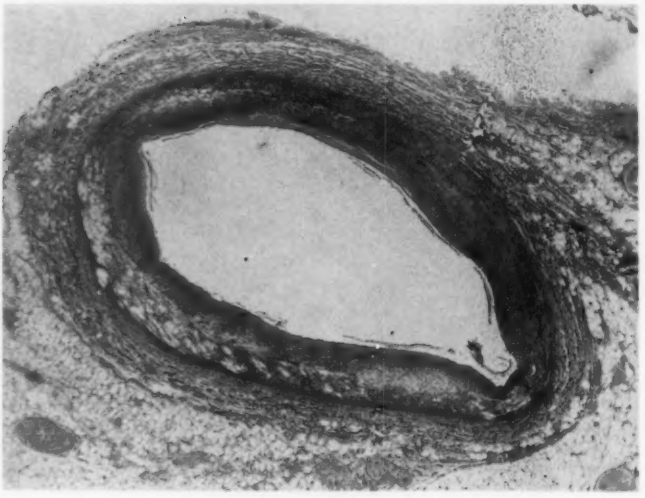


Fig. 5 (Case 2).—Section of coronary artery, showing moderately diffuse changes of medial cystic degeneration. Mallory's phloxine methylene blue stain; reduced approximately 35% from mag. × 30.

with bilateral hydrothorax of 200 ml. each; acute passive congestion of abdominal viscera; minimal atherosclerosis of aorta and coronary arteries; remote hysterectomy.

Abstracts of Three Additional Cases

Lesions of cystic medial degeneration confined to the coronary arteries were incidental findings in three cases. Since these lesions were not associated with dissecting aneurysm and not related to the clinical symptomatology or cause of death, each of the three cases will be presented briefly.

CASE 2.—The first of these three cases was that of a 48-year-old white woman who was admitted to the hospital in September, 1956, for terminal care of metastic breast carcinoma. In 1950, she underwent a left radical mastectomy, and since 1951 she had received considerable x-ray therapy.

Grossly, the coronary arteries were not remarkable except for minimal atheromatous changes histologically; however, there was extensive replacement of the normal architecture of the media by discrete and confluent foci of myxomatous change with marked cystic degeneration (Figs. 5 and 6). These changes often involved the entire thickness of the media, but more often the focal

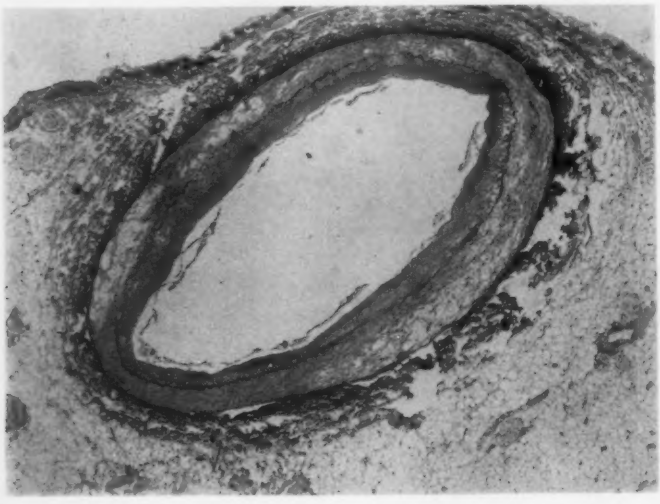


Fig. 6 (Case 2).—Section of coronary artery, showing moderately diffuse changes of medial cystic degeneration. Verhoeff's elastic tissue stain; reduced approximately 35% from mag. × 30.

lesions were most marked in the outer third of the media. The medial lesions previously referred to as areas of myxomatous change with cystic degeneration were composed of persistent and sparse medial elements (fibrocytes, smooth muscle cells, and fragmented collagen and elastic fibers) separated from each other by varying amounts of faintly acidophilic "ground substance." A striking feature was the complete absence of an inflammatory-cell infiltrate. The intima exhibited slight fibrous thickening, and no changes of note were present in the adventitia.

CASE 3.—The second of the three cases was that of a 57-year-old white woman, admitted to the hospital in January, 1957, with a week's history of abdominal pain and distention, vomiting, and absent bowel movements. On admission the patient was comatosed and in shock; she died three hours later. Autopsy revealed an obstructive anaplastic carcinoma of the splenic flexure, with gangrene and perforation of the transverse colon with acute peritonitis.

Save for slight to moderate focal atherosclerosis, the coronary arteries were not grossly remarkable. Histologically, sections of coronary artery showed fibrous intimal thickening without significant narrowing of the lumens. Changes consistent with medial cystic degeneration were represented essentially by focal replacement of the normal architecture of the media by "myxomatous tissue." In these areas there was a fine fibrillary network with scattered stellate fibrocytes. The interstices formed by the fine fibrillary network were of varying sizes and contained degenerating smooth muscle cells and distorted, disoriented, elastic fibrils (Fig. 7).

CASE 4.—The third of the three cases was that of a 68-year-old hypertensive Negro woman admitted to the hospital in October, 1957, with a clinical diagnosis of cerebrovascular accident. She

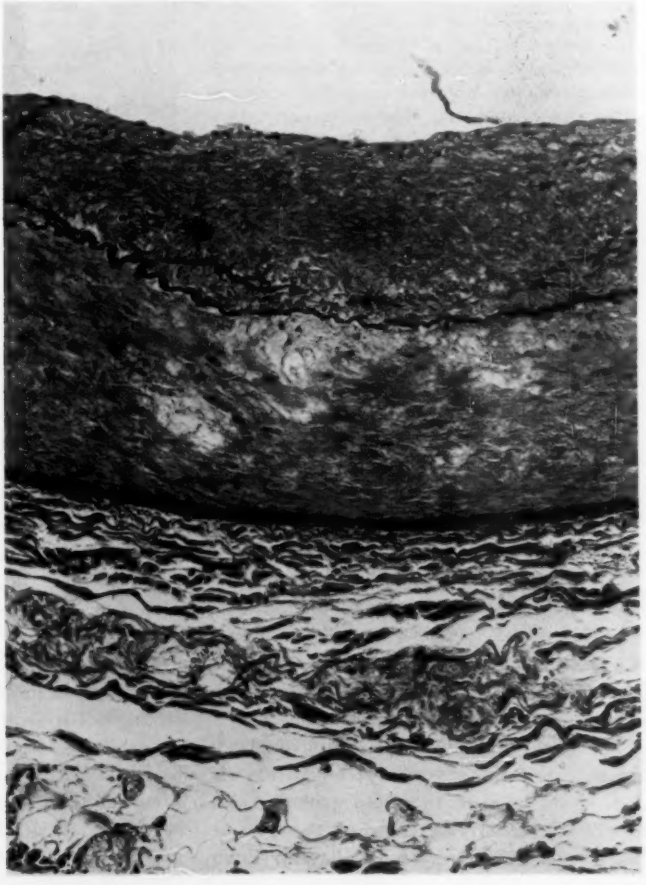


FIG. 7 (Case 3).—Section of coronary artery, showing small foci of medial cystic degeneration. Verhoeff's elastic tissue stain; reduced 10% from mag. × 200.

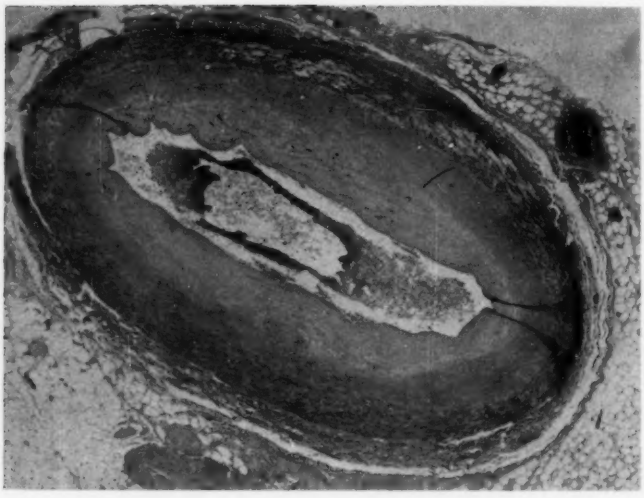


Fig. 8 (Case 4).—Section of coronary artery, showing discrete and confluent foci of medial cystic degeneration and moderately marked fibrous intimal thickening. Aniline blue stain; reduced 35% from mag. × 30-35.

remained comatose and died on the second hospital day. Autopsy revealed an intracerebral hemorrhage with intraventricular extension. Additional findings were as follows: Follicular carcinoma of thyroid gland with pulmonary metastasis, generalized arteriosclerosis, hypertensive heart disease, and medial cystic degeneration of coronary arteries.

Gross examination of the coronary arteries showed few atheromatous plaques, and lumens were not considered to be seriously compromised. Histologically, sections of coronary artery showed moderately marked atherosclerotic intimal changes and foci of media cystic degeneration (Fig. 8) observed in the several levels exhibited a striking similarity to the cases previously described.

Comment

It is commonly stated that cystic medial degeneration is limited to the aorta and does not generally extend into its branches. The finding of cystic medial degeneration limited to the coronary arteries is most unusual. One of our cases of coronary involvement alone was similar to the case reported by Lovitt and Corzine,[1] presenting the full complement of the lesion, i. e., cystic medial degeneration associated with a dissecting aneurysm.

Admittedly, the status of Uehlinger's two cases is doubtful. Nevertheless, an associated lesion of medial cystic degeneration as a probable underlying cause of the dissecting coronary aneurysm in each of his two cases might well be considered. In neither of his two cases was there significant coronary atherosclerosis. The absence of such changes is of some significance, since a small percentage of aortic dissecting aneurysms are attributed to atherosclerotic damage of the aorta. Nor was there any morphological evidence of an acute necrotizing coronary arteritis, as was probably the basis for the case reported by Homma and Yenikomshian.[3] Also to be considered is the fact that the dissecting aneurysms were spontaneous and not traumatic, as was, for example, the case reported by Hedinger.[4] Indeed, in cases of medial cystic degeneration of the aorta with dissecting aneurysm, not all sections of aorta will show changes of medial cystic degeneration, and sections taken at the level of the dissecting aneurysm itself may often fail to reveal these changes, since they may be obscured by the dissecting aneurysm. Even in our case, while segments of coronary artery adjacent to the dissection had typical lesions of medial cystic degeneration, sections through the dissecting aneurysm itself revealed only a solitary minute focus of medial change.

The similarity between these coronary lesions and those classically affecting the aorta is striking. The latter have been extensively investigated by several authors: Moritz,

Sailor, Gore and Seiwart, Gore, Halpert and Brown, Burchell, Whittaker and Sheehan, Bean and Ponseti, Baer, and Beaven and Murphy.[6-14] Essentially, the lesions of cystic medial degeneration consist of an increase in ground substance with degeneration and destruction of medial components (smooth muscle fibers, collagen, elastic and reticular fibers) in varying proportions. The persistent fibrocytes may assume stellate forms and the focus of degeneration is loosely referred to as "myxomatous tissue." With further destruction of medial elements and increase in ground substance cystic formations occur. Healing is slow and not accompanied by dense scar tissue, and so the affected area is always a point of weakness. Little or no inflammatory-cell infiltrate is seen, and the vasa vasorum presents little or no significant alteration at this stage, i. e., prior to the formation of a dissecting aneurysm. It is believed that this set of conditions predisposes to rupture of the vasa vasorum and consequently to intramural hemorrhage and a dissecting aneurysm. Fundamentally, a disorder of the ground substance is postulated, due possibly to an inborn error of metabolism, some hormonal imbalance, or dietary or toxic factors.

Characteristically, the dissection occurs between the inner two-thirds and outer one-third of the media. External examination of the affected coronary artery or arteries may at first prove misleading, since congenital and acquired true aneurysms may simulate this picture. However, a dissecting aneurysm involves a much greater segment of coronary artery. For comprehensive and recent reviews on aneurysms of the coronary arteries, the reader is referred to the papers by Packard and Wechsler [15] and by Crocker, Sobin, and Thomas.[16] Extensive subintimal hemorrhages in the coronary arteries (Wartman, Paterson, Horn and Finklestein, and Drury [17-19]) may grossly simulate a dissecting hemorrhage into the media but should be readily differentiated by microscopic examination.

The symptomatology in our case of dissecting aneurysm of the coronary arteries differs very little from other causes of acute coronary occlusion. Death may follow immediately with signs of coronary insufficiency (Lovitt and Corzine [1]) or may be delayed for a few days with characteristic electrocardiographic changes of evolving and expanding myocardial infarct. There appears to be no clinical clue that would lead to a diagnosis of a coronary dissecting aneurysm, although some importance has been attributed to a history of physical stress one to several days preceding the clinical picture of coronary occlusion (Uehlinger,[2] Lovitt and Corzine [1]).

The case of coronary medial cystic degeneration with dissecting aneurysm presented in this paper is the second in which both lesions have been described. The two cases of dissecting aneurysm of the coronary artery reported by Uehlinger may have a similar pathogenesis, as, indeed, may prove to be the case with most idiopathic coronary dissecting aneurysms.

Summary and Conclusions

A case of dissecting aneurysm associated with changes of medial cystic degeneration confined to the coronary arteries is presented. The clinical picture was that of an acute coronary occlusion with electrocardiographic changes commonly seen in an evolving and expanding myocardial infarction. Even in retrospect there appears to be no clinical clue leading to the diagnosis of coronary dissecting aneurysm. Although some importance has been attributed to a history of physical stress occurring one to several days before the onset of clinical symptoms, the available clinical data of our case did not bear this out. A review of the literature shows this case report to be the second in which both lesions, i. e., medial cystic degeneration and dissecting aneurysm, were present and confined to the coronary arteries.

Three additional cases are briefly presented of medial cystic degeneration of coro-

nary arteries occurring as incidental findings at autopsy. These incidental findings suggest that so-called idiopathic dissecting aneurysm, even of the coronary arteries, may well be due to medial cystic degeneration.

Dr. S. L. Robbins provided criticism and Mr. Leo Goodman made the microphotographs. Dr. Henry Baker served as clinical consultant.

Mallory Institute of Pathology, Boston City Hospital (18).

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An Experimental and Statistical Method in the Study of New Drugs

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The problem of relating the effectiveness of the enormous number of new drugs now being produced by the pharmaceutical houses to existing medications is exceedingly difficult. It is, however, imperative that they be evaluated in this respect and that they be integrated correctly into the therapeutic armamentarium. The preliminary work begins with the chemist and the pharmacologist and proceeds to the physiologist, as well as to the field of animal experimentation. Throughout this period, new drugs are screened for toxic reaction and pharmacologic effect.

The obvious way to test the value of a medication is to give it to patients with the required symptoms and observe the results.[1] A strict procedure of checks and controls must be inaugurated and carried out, which will permit conclusions which are free of the variabilities of the subjective impression, except in cases where a medication produces a markedly obvious change, and even in this type of medication controls are necessary. The value of controls lies in the fact that many variables are involved both in the clinical observations and in the therapeutic interpretation of the clinical effect of drugs in humans. Subjective clinical observations are difficult to evaluate; the degree of pain, the amount of relaxation, the sedative effect, or the well-being of a person must all be placed on a reasonable measuring scale.

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University Health Services Harvard University (Dr. Cass); 20 Grantland Rd. (Dr. Frederik).

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I. General Principle

It is the purpose of this paper to set forth the four basic premises forming the fundamental procedure in the clinical study of a new drug. However, since these premises are deceptively simple, the paper will present the application of the principles in the form of an actual clinical case study illustrating the experimental and statistical methods employed within the framework of the premises. The four basic premises are as follows:

1. Careful design of the experiment
2. Adequate clinical observations
3. Statistical evaluation of the findings
4. Clinical report

Each of these premises requires a breakdown into its component parts, dividing the experiment into numerous phases which, taken together, make for an assessment of the drug under study which comes as close to the objective facts as possible.

1. *Design of the Experiment.*—A careful design of the experiment is decisive for its outcome. The data collected must be meaningful, truthful, comparable, and expressed in numbers so that they can be subjected to statistical analysis. The 10 points to consider in setting up the experiment are as follows:

A. *Precise definition of the objective of the study and limitation,* for practical reasons, to the most important clinical effects.

B. *Establishment of a numerical scale of measurement* which is necessary for the mathematical analysis of the data.

C. *Use of an ineffective placebo and a standard of known and accepted effectiveness.* Sometimes the medication to be tested is given in two or three doses in order to

establish a further control in that a gradation in effectiveness should be found in reference to the standards if the medication is to be considered effective.

D. *Use of triple-blind technique,* which stipulates that all medications are provided as unknowns and identified only by code numbers. The general type of the drug under study must, however, be known to the investigators, who need this information for setting up the experiment.

E. *Random sequence* of the medications, which is essential in that no one medication follows another in administration any more frequently than any other medication. Should this occur, the carry-over of the most effective medication could influence the effectiveness of the weaker medication.

F. *Number of daily observations and length of test period of each medication.* It is evident that these depend on the effect of the medication. In other words, a medication of short effect should be observed shortly after administration and repeated, both in administration and observation, several times during the 24-hour period. When accurate observations of duration of the effect of the medication are required during the comparison of drugs of varying duration of action, it is sometimes necessary to interject placebos at intervals after the administration of the effective medication. The test period of short-acting medications, such as analgesics and antitussives, is usually one week, and the frequency of observations, three times a day. No rigid rule can be established, since the procedure to be followed depends on the problem under investigation. In those cases in which a medication is designed to relieve discomfort in the patients, it appears not permissible to subject patients to placebo medication and drugs of uncertain action for a prolonged period.

G. *Total duration of study.* The total duration of the study will equal the total number of test periods, which is equivalent to the number of unknowns times the test period. This, of course, is true only when the medication of patients is started and discontinued on a set schedule, a technique which is advantageous because the number of variables increases when the study is unduly extended. A concentrated schedule tends to compensate for the variabilities introduced by visiting periods, weather changes, and variations in symptoms of the disease, and since the majority of other factors are weeded out by the internal controls, an effective interpretation of data is possible.

H. *Number of test subjects.* This number should approach, in the ideal study, the factorial of the number of unknowns, especially when the clinical difference between the medications is expected to be small. This principle narrows drastically the number of unknowns which can be handled effectively. In a previous study, we attempted to determine the clinical differences of nine unknowns, utilizing not over 120 patients.[2] In a study with five unknowns the factorial of five equals one, times two, times three, times four, times five, or 120 patients. Since it is frequently difficult to obtain this number of patients, a compromise may become necessary, but 50% of the required patients is desirable.

I. *Number of individual observations.* In any study these will automatically equal the number of unknowns times the number of patients, times the number of daily observations, times the number of days in the observation of each number. The total observations will be adequate for meaningful statistical evaluation if the number of daily observations and the length of the test periods for each medication were adapted to the objective of the project.

J. *Objective reporting.* This can be achieved when both the observer and the investigator realize that they must be disinterested in the results. This is to be carried to the point where all concerned report all material objectively as it is determined and discuss only the results and, in general, the interpretation of the data. Why a medication does or does not stand up under the

study is not a matter of issue; once the medication is subjected to this type of study it must be acknowledged that it does or does not demonstrate its value as evaluated by this technique. In actual practice, these studies must be controlled so rigidly that it is obviously impossible for the investigators to influence the results in any way. In some studies, because of the small variations in the clinical effect of the medications, it is quite possible that inconclusive or ambiguous conclusions may be reached. The differences may be so small that no one medication is dominant except the drug of known effect. The unknowns may, on the other hand, be either indistinguishable from the placebo or of the order of effect of the standard. Where placebo and standard are found in their correct position, it is regarded safe to assume that the clinical differences of the unknowns lie in the effectiveness of the tested unknown medications.

2. *Clinical Observations.*—The clinical observations are recorded either by one or a multitude of observers. There are advantages to having a single observer in that the interpretation of the clinical changes varies in each person. In principle, it is well, too, to have the observer dissociated entirely from the design of experiment and compilation and analysis of data. The coordinator of the project may actively participate in collecting data in order to obtain his personal impressions of side-effects, but it is preferable that all conclusions be drawn from the mathematical analysis of the observed data as recorded by a trained but disinterested observer. Where a scope of a study is such that a single person is unable to make all the observations, strict coordination between the observers or institutions taking part in the experiment is required. The objective of the study must be uniformly understood and the general field of investigation understood by all involved. When the clinical variations are clearly demonstrated and the above requirements are fulfilled, the distribution of a project over several institutions and independent observers is not only permissible but may enhance the objectivity of the total findings and render more valid the final conclusions.

As a rule, the clinical observation is concerned with the desirable, as well as unde-

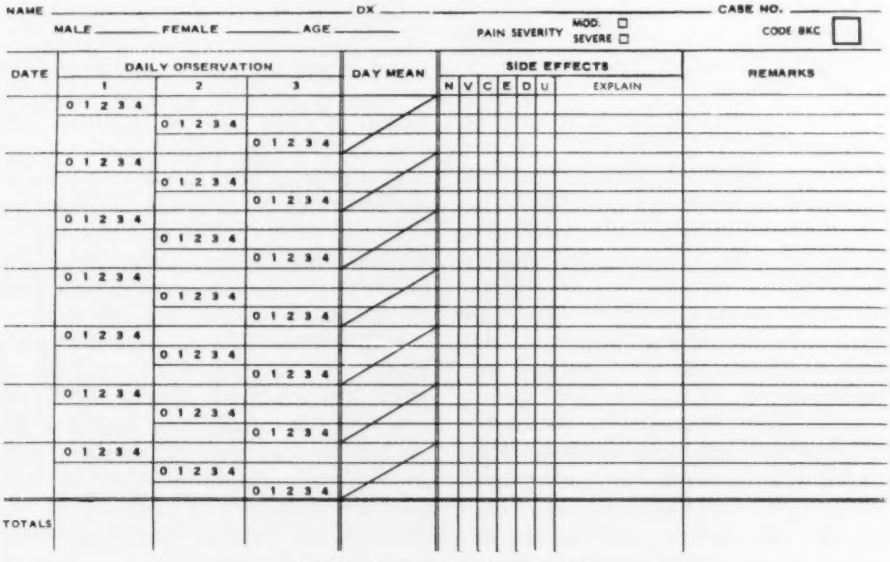

Fig. 1.—Protocol card, front side.

DIRECTIONS:

Report Degree of Relief as:

0 = No Relief

1 = Very Slight

2 = Moderate Relief

3 = Still has some pain (Almost Complete)

4 = Complete

Report Side Effects:

N = Nausea (if vomiting, Note under Explain)

V = Vertigo or Dizziness

C = Constipation

E = Excitement

D = Drowsiness

U = Euphoria

Note under Remarks: Any other medications given, spontaneous statement and/or remarks of patient, and actual vomiting, cramps, or diarrhea. Note also any pertinent information concerning type of pain. Elaborate in a precise manner on every side effect recorded with comment of Resident on abnormal physical findings. Give reason for omitting drug when this is done. Use space below for comments.

Fig. 2.—Protocol card, reverse side.

sirable, action of the drug under study. Exploration of the principal action may be affected by direct questioning, since the observer has to explain to the patient the purpose of the new medication. Information on side-effects, by contrast, is not solicited. Side-actions are reported only when expressed spontaneously without direct questioning of the patient. Objective data, e. g., laboratory studies, are collected if necessary and recorded together with the other findings.

Uniformity of clinical reporting is ensured by the use of protocol cards which are drawn up by the project coordinator. A sample of these is shown in Figures 1 and 2. The front side (Fig. 1) presents the data as recorded in agreement with the directions printed on the reverse side (Fig. 2). The cards can easily be adapted to the particular requirements of each study, but in every instance the intensity and frequency of the clinical changes must be expressed as a numerical value which alone can be employed for a statistical work-up. At the end of the study the numerical values of the clinical observations are totaled and averages for various times of day, each day, and the total test period of each code, established.

3. *Statistical Evaluation of Findings.*—When compiled, the total number of observations are presented in the form of tables. There is a definite advantage in large numbers of observations in that a smaller difference in the clinical variations may be defined by these statistical methods. The tables, in turn, constitute the basis for diagrams, curves of effectiveness, and other types of graphic illustrations. The figures from which the graphs are drawn are tested for significance by the *t*-test, variance analysis, and other statistical techniques applicable to the specific needs and design of the particular study. These various types of tests and methods have been discussed in detail in previous publications.[3]

In many instances the prime action of the drug under study, but not its side-actions, is the target of the mathematical analysis. These latter are evaluated by statistical techniques in order that a picture of such effects be recorded as incidentally obtained. Frequently, a more prolonged study is required to bring out the side-effect liability of a new agent in comparison with a known drug. In cases of severe toxicity, e. g., depression of the white or red hemopoietic system, a numerical determination of the significance of this occurrence is not necessary because even a limited incident of deleterious blood changes will deter from the introduction or use of a new drug.

4. *The Final Clinical Report.*—Having rated the various unknowns by their clinical effect, it is now permissible to request the code. In the ensuing final clinical report the facts obtained from the statistical evaluation of the accumulated clinical observations are presented and discussed. In the ideal case, one will find a precise agreement between the clinically observed increase in

effectiveness and the increase in dosage of the medication; in other words, the placebo will show up at the least effective level and the largest dose, at the most effective level. There is, however, a plateau tendency as the dose approaches the maximum effect.

The specific numerical results in each study are pertinent for that one only. The actual numerical values compiled by the same technique in a different study of the same agent and dosages are not necessarily identical. A study by the same observer on the same group of patients at another time might produce a wider or narrower range, and the results might be equally reliable. Beyond the actual facts established, no valid conclusions can be drawn.

Much discussion has been had with regard to the principle of placebo reactors in clinical studies. There is no place in an impartial study for the arbitrary removal of certain patients because they do not respond as anticipated. Patients tend to respond differently at different times,[4] and although results may be diluted by those patients who either over- or under-react, this is a psychological-physiological phenomenon and must be included as a variable. It is recognized that there is a very small percentage of persons that fail to respond, or over-respond, to medications, but when there is a clear-cut clinical symptom, this percentage is extremely small.

II. Case Study

The case study illustrating the application of the principles set forth above was conducted with the oral dosage form of dihydrocodeine bitartrate. The substance, supplied in the form of bitartrate tablets (Rapacodin *), had been prescribed for many years as an antitussive in Europe and South America, but its analgesic action escaped notice. Recently, Gravenstein and associates,[5] in this country, studied dihydrocodeine in humans and found that 30 mg. of the bitartrate salt given subcutaneously afforded pain relief with little if any side-effects. Since the work of Gravenstein and associates was limited to the parenteral preparation, an assessment of the analgesic action of orally administered dihydrocodeine appeared to be in order.

1. *Design of Experiment.*—The prime objectives in this example were (1) to determine the analgesic action of dihydrocodeine bitartrate and (2) to determine the usable dosage of this drug. The secondary objective was to observe side-effects occurring with the doses under trial. Side-effects were simply recorded as being present or absent. The time of onset and the duration of the effect were not studied.

The test included a placebo and codeine phosphate, 60 mg. The dosages of dihydrocodeine bitartrate under study were 30, 45, and 60 mg. All medications were designated by code numbers (A, F, G, K, and M) known only to their supplier. A sealed copy of the code was left with the coordinator of the study, to be opened in case of an emergency. The coded drugs were administered in random sequence, each code number being given three times daily for a period of one week. It was possible in this trial series to start and discontinue simultaneously the medications of all test subjects. The total duration of the study thus was equal to the number of codes under trial, i. e., five weeks. Eighty patients, which is better than 60% of the factorial (one hundred twenty), were started with the test medication, and sixty-one completed the study. The drop-outs were not caused by the medication. The total number of individual observations equaled 6405, an adequate number for meaningful evaluation.

2. *Clinical Observations.*—The clinical trial was conducted at Long Island Hospital, Boston. All of the patients included in the study suffered from chronic diseases, having various degrees of discomfort, but most of them were in moderately severe or severe pain. Cases, for the most part, were those with a diganosis of chronic and rheumatoid arthritis, malunion of fractures, and

* Knoll Pharmaceutical Company, Orange, N. J.

TABLE 1.—*Averages for the Coded Drugs*

Drug Code	8 a.m.	12 Noon	4 p.m.	Day 1	2	3	4	5	6	7	Wk. Average
A	1.206	0.946	0.906	1.803	1.322	0.962	0.814	0.667	0.820	0.749	1.020
G	2.801	2.782	2.742	2.350	2.656	2.749	2.803	2.945	2.973	2.951	2.775
F	2.164	2.237	2.166	2.290	2.200	2.213	2.164	2.153	2.169	2.137	2.189
K	1.885	1.867	1.773	1.934	1.869	1.820	1.809	1.770	1.869	1.820	1.842
M	2.761	2.731	2.679	2.158	2.574	2.672	2.869	2.913	2.869	3.011	2.724

other traumatic conditions. In a great percentage of patients the pain was caused by chronic inflammatory conditions of the rheumatic type. This is a factor to consider when analgesics are studied which are combined with salicylates or other antiphlogistic or antirheumatic principles. In the present trial no anti-inflammatory agents were involved, and the observations were exclusively concerned with pain relief of an unspecific nature.

The statements of patients after each medication were recorded on the observation card shown in Figures 1 and 2. The degree of pain relief was expressed as numbers in five gradations. The observations were totaled on each card, and the average effectiveness at 8 a. m., 12 noon, and 4 p. m., calculated. In addition, the average effectiveness for each day of the week and the over-all effectiveness of the total week were established. In Table 1 these averages are shown for each of the five coded drugs.

TABLE 2.—*Side-Effects Observed During the Trial Period* *

Code	N	V	C	E	D	U	Di	Cr	Vo	Patients, No
A	10	—	—	—	—	—	11	4	6	9
K	3	—	2	—	2	—	2	—	3	4
F	—	—	5	—	—	—	1	—	—	4
G	3	—	3	—	—	—	—	1	2	4
M	10	—	9	—	—	—	—	1	5	8

* N indicates nausea; V, vertigo; C, constipation; E, excitement; D, drowsiness; V, euphorid; Di, diarrhea; Cr, cramps; Vo, vomiting.

Side-Effects: The following side effects were considered as possible: nausea, vertigo, constipation, excitement, drowsiness, diarrhea, cramps, and vomiting. Since each side-effect might theoretically have occurred after each medication, the potential num-

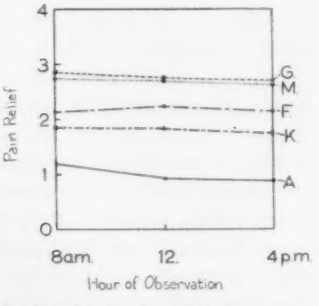

Fig. 3.—Graph of pain relief during one day.

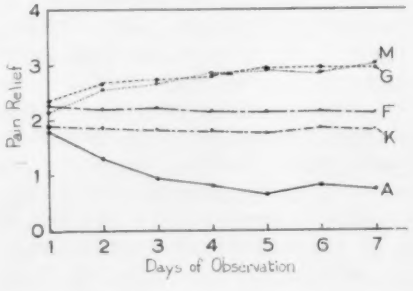

Fig. 4.—Graph of pain relief during one week.

TABLE 3.—*Relative Clinical Effect of the Coded Medication*

Rating	Code		
1	A	=	1.020
2	K	=	1.842
3	F	=	2.189
4	M	=	2.724
5	G	=	2.775

Drugs ranked according to their effectiveness as analgesics:
A least effective
G most effective

TABLE 4.—*t-Values for the Five Codes*

Code Compared	*t*—Value		Probability		
A—K	6.03				
A—F	8.62				
K—F	28.16				
F—M	4.17	*t*=value	0.05	0.02	0.01
			2.45	3.14	3.71
G—M	1.51	DF=6			
G—F	5.75				

ber of each side-effect could equal the total number of observations. Actually, the reported side-effects were negligible, with all code numbers as recorded in Table 2.

3. *Statistical Evaluation of Findings.*—To present the analgesic action of the substances under study, the accumulated data were expressed as graphs (Figs. 3 and 4) derived from the numbers listed in the previous section (Table 1). Figure 3 illustrates the degree and course of pain relief during the day; Figure 4 presents the data of the entire week. The graphs indicate that a relatively ineffective medication was tested against a relatively effective one, but none of them had an either total positive (4) or negative (0) effect. The ranks of the drugs according to their relative clinical effect as analgesics are demonstrated in Table 3. In our scale, A received the lowest rating and G, the highest. Since A was the lowest in effectiveness in the scale, we had to determine whether or not the next drug in the clinical scale (in this case, K) was significantly superior as an analgesic to A, and so on for each contiguous pair of medications in the clinical scale.

TABLE 5.—*Administrative Schedule*

Dose, Mg.	Patients, No.	Males	Females	Average Time, Days
20	26	21	5	18.4
40	31	21	10	13.9
60	50	39	11	13.7
Total	107	81	26	

The clue to the statistical significance of our findings was provided by the *t* values presented in Table 4. The *t* values were obtained by comparing the day values of the various codes. The figures reveal that K was significantly superior to A; F, significantly superior to A and K, and K and M, significantly superior to F, K, and A. The study did not show a significant difference between the analgesic effectiveness of the drug, M and G ($t=1.51$).

4. *Final Clinical Report.*—Having established the statistical significance of the difference in efficacy between the various code numbers, the code was broken and the drugs and dosages revealed as follows:

A=Placebo
K=Dihydrocodeine bitartrate, 30 mg.
F=Dihydrocodeine bitartrate, 45 mg.
M=Codeine phosphate, 60 mg.
G=Dihydrocodeine bitartrate, 60 mg.

In this study, a direct proportion existed between the recorded and calculated efficacy of the test substances and their phar-

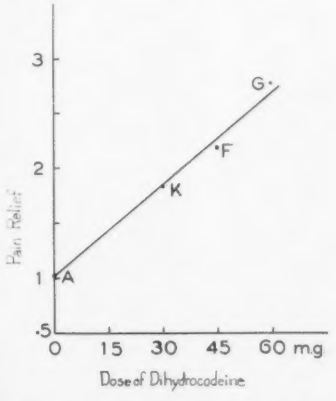

Fig. 5.—Dose response curve of dihydrocodeine bitartrate.

TABLE 6.—*Results*

Dose, Mg.	Side-Effects, No. Patients							Total	Average/ 100 Patient-Days
	Nausea	Vomiting	Constipation	Excitement	Drowsiness	Unsteady	Shaky		
20	3	2	7	1	5	1	0	19	3.97
40	11	7	9	0	9	1	7	44	10.23
60	19	14	21	3	17	0	2	76	11.11
Total	33	23	37	4	31	2	9	139	

Table 6 lists the number of patients and the side-effects as indicated.

macologic action and dosage. The only medications which did not significantly differ from each other were the 60 mg. doses of dihydrocodeine and codeine. This indicates that at this level dihydrocodeine and codeine were equipotent.

The decoded variables, except for the codeine, were plotted in the form of a dose response surve (Fig. 5) designating the lowest ranking medication (placebo) as the "0" mg. point. The numerical variation of pain relief from 1.0 to 2.8 represented a good range of value within which it was possible to differentiate easily the medications.

The four points presented on the dose response curve were practically on a straight line, and their position on this line indicated that within the dose range under study the analgesic action of dihydrocodeine was approximately proportional to the increase in dosage. It cannot be inferred, however, that a further rise of the dose level would have led to an increased analgesic effect, although this is possible. Additional studies are necessary to determine the full range of the analgesic efficacy of dihydrocodeine and the eventual shape of the dose response curve.

Both the position of the placebo at the least effective level and the increasing effectiveness of the dihydrocodeine indicate good control as well as good clinical effect. The method has proven adequate in determining the analgesic action of orally administered dihydrocodeine bitartrate in the dose range from 30 over 45 to 60 mg. It was also established that in this dose range the substance has a low side-effect liability and, thus, all characteristics of a useful analgesic.

Summary

The principles of a new drug study with use of placebo and triple-blind technique is described as it was applied to the actual testing of dihydrocodeine as an oral analgesic. The analgesic effect of orally administered dihydrocodeine on a group of patients was established as follows:

1. Dihydrocodeine bitartrate (Rapacodin) in each dose level studied has a significant analgesic action as compared to a placebo.
2. A 60 mg. dose of the substance is superior in its action to 45 mg. and 30 mg.
3. A 45 mg. dose provides more analgesic action than 30 mg. of dihydrocodeine.
4. A 60 mg. dose of codeine HCl and 60 mg. of dihydrocodeine have for all practical purposes an identical analgesic affect on this group of patients.
5. Side-effects were negligible.

Addendum

Report on Dihydrocodeine Bitartrate in Combination with APC *

At a recently completed clinical trial it was found that dihydrocodeine bitartrate was an effective analgesic on chronic moderate pain in dosages of 20, 40, and 60 mg. Each medication was given for a period of seven days, and all patients received all medications in random rotation. Side-effects were found to be negligible in the lower dosages and slight in the larger.

* In this study the APC combination consists of 200 mg. of acetylsalicylic acid, 150 mg. of acetophenetidin, and 30 mg. of caffeine.

Since a complete picture of the side-effects was necessary for an adequate understanding of the drug, it was decided to administer the medications to a number of patients for 30 days, or as tolerated, in the dosage schedule of 20, 40, and 60 mg. in combination with APC, as it was intended that this combination be the final marketed preparation.

A total of 107 patients received the medications: Of these, 26 patients received 20 mg. with APC; 31 patients received 40 mg. with APC, and 50 patients received 60 mg. with APC.

Conclusions.—Contrary to the previous experience, extensive side-effects were found in the higher dosage levels. In some cases these occurred within 24 hours, and in the others, within 3 to 5 days. Many patients were unable to tolerate the large dosage for the entire 30 days. The chief side-effect was vertigo; occasionally there was itching, and rarely, nervousness. One patient suffered vertigo to a degree that he he fell and was injured in the fall.

The enhancing of the analgesic as well as the side-effects of codeine by APC has been noted and reported upon frequently by ourselves and other workers.

Tables 5 and 6 show the actual administrative schedule and the results demonstrated in this clinical investigation.

Table 5 shows the number of patients who received dihydrocodeine bitartrate in dosages of 20, 40, and 60 mg. with APC. It also presents the sex distribution. The last column shows the average time that the drug was taken. The maximum time was 30 days.

Table 6 lists the number of patients and the side-effects as indicated.

Harvard University, University Health Services, 51 Holyoke St. (38).

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Case Reports

Hemophilus Pyarthrosis in an Adult

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Hemophilus influenzae is rarely the causative organism of suppurative arthritis or infection in general in adults.[1] A review of the literature reveals that Hemophilus pyarthrosis occurs more commonly in infants and in many cases is associated with meningitis. Infections with this microorganism other than pyarthrosis have been successfully treated with incision and drainage, and with every antibiotic in current use. The accompanying Table outlines the pertinent data from the literature.

It is our purpose to present the case of the second adult patient with Hemophilus influenzae pyarthrosis.

Report of Case

The patient, a 48-year-old Negro laundress, was admitted on Dec. 4, 1956. Her chief complaint was a painful left shoulder and ankle joints of six days' duration. She had been well until the onset of an upper respiratory infection about two weeks prior to entry. Eight days later the left shoulder and ankle joints became hot, red, tender, and swollen. She had a nonproductive cough, low-grade fever, and coryza in addition to the joint symptoms. Symptomatic treatment at home was palliative but gave no prolonged relief. The joints became progressively more enlarged, and she was unable to leave her bed on account of the pain and swelling. She noticed general malaise but no chills.

Physical examination revealed an obese, well-developed Negro woman, appearing her stated age. She was in acute distress, perspiring profusely, and unable to move in bed or sit upright without initiating excruciating joint pain. The temperature was 103.5 F, heart rate 104, respiratory rate 36, and blood pressure 140/76. The skin was moist, red, and warm over the left shoulder and ankle joints. There were no petechiae or hemorrhages. The posterior pharynx was inflamed. The breasts were large and pendulous. Diffuse moist inspiratory rales were heard over the posterior lung fields, bilaterally. There was a harsh Grade 2 systolic murmur at the apex. Movement of the left shoulder joint was limited to 75 degrees abduction. The heat from the joint extended distally midway to the elbow on the dorsolateral surface of the arm.

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Hemophilus Pyarthrosis in Thirty Infants and One Adult (1899-1957)

Number and Age Range of Patients	Joint Involved	Complications	Therapy	Died	Recovered	No Details	References
2 infants under 24 mo.	Ankle	Septicemia & meningitis	Incision & drainage	1	--	1	2,3
3 infants under 12 mo.	Shoulder	Septicemia & meningitis	Incision & drainage	1	--	2	4-6
11 infants and 59-year -old adult	Knee	Septicemia & meningitis	Incision & drainage; sulfadiazine	2	9	1	7-15
5 infants under 12 mo.	Elbow	Septicemia & meningitis	Incision & drainage; chlortetracycline	2	2	2	16-20
An infant	Wrist	Meningitis	Incision & drainage	--	--	1	21
7-month-old infant	Hip	None	Incision & drainage	1	--	--	11
3 infants under 12 mo.	Multiple	Septicemia & meningitis	Incision & drainage	1	--	2	11,15,22
4 infants under 24 mo.	Not specified	Septicemia & meningitis	Incision & drainage	2	--	2	23-36

There was 1+ pitting pretibial edema of the right leg, and stiffness, painful movement, and limitation of motion of the right knee joint. The left ankle joint was red, swollen, hot, and tender to palpation, and there was 1+ pitting ankle edema. The remainder of the physical examination was not remarkable.

Admission laboratory studies included urinalysis, which showed a specific gravity of 1.013, 3+ proteinuria, and several white and red blood cells per high-power field. The hemoglobin was 11.5 gm./100 ml.; hematocrit 33%, total white blood cell count 35,150, with a differential of 80% polymorphonuclear leukocytes, 3% band forms, 14% lymphocytes, and 3% monocytes. The corrected sedimentation rate was 38 mm. in one hour. The serology was negative. Aspiration from the left shoulder joint yielded a purulent, pink exudate from which a pure culture of Hemophilus influenzae, Type B, was grown. Aspirations from the left ankle and right knee joints were productive of nonpurulent joint fluids, which were negative on culturing. Blood, sputum, and urine cultures were negative. Subsequent urinalyses on the 7th and 14th hospital days were negative. Admission and repeated chest roentgenograms revealed only hilar nodular densities. Roentgenograms of the left shoulder were negative initially, but after five weeks' hospitalization subsequent films revealed a small area of increased radiance just proximal to the greater tuberosity of the humerous on the lateral aspect. The corticalis in this area was apparently missing, and was thought to represent an early inflammatory process. Roentgenograms of the left ankle initially were negative also but in the fifth week revealed soft-tissue swelling around the lateral malleolus, and a deformity of the os calcis was suggested. This was thought to represent an old healed fracture of the calcaneus with depression of the fragment. Her temperature chart revealed an intermittent febrile course during the seven days of tetracycline therapy, and, subsequently, the first seven days of combined chloramphenicol-dihydrostreptomycin therapy. Repeated blood and joint aspiration cultures on the 7th and 14th days were negative.

Therapy consisted of bed rest, physical therapy, and antibacterial chemotherapy. The last consisted initially of tetracycline, 500 mg., P. O., every six hours. This was continued for seven consecutive days, when the report of the positive culture from the joint was received. In view of her clinical course, the tetracycline was discontinued, and combined therapy was initiated with chloramphenicol, 500 mg. P. O. every four hours, and dihydrostreptomycin, 500 mg. I. M. every six hours. The dihydrostreptomycin was discontinued after 14 days' therapy, when the patient had been afebrile for seven days and had shown progressive clinical improvement. The chloramphenicol was discontinued after 24 days' continuous therapy. The infection of the posterior pharynx disappeared after four days of tetracycline therapy. The lung fields were clear to percussion and auscultation after 24 hours' hospitalization.

The total white blood cell count rose on the sixth day of tetracycline therapy to 42,500 per cubic millimeter, with a differential count similar to that obtained on admission. The sedimentation rate remained 36 mm. in one hour during the first week, and the hematocrit dropped to 31%. Two days after the initiation of combined treatment with chloramphenicol and dihydrostreptomycin, the total WBC fell to 20,800, and the patient started to show objective and subjective signs of improvement. After 7 days of combined therapy the WBC was 16,300, the hematocrit 34%, and E. S. R. 30 mm. The day prior to discontinuance of dihydrostreptomycin, the WBC was 9500, with a normal differential, and the hematocrit 35%. The day prior to discontinuance of chloramphenicol the WBC was 6700, the hematocrit 32%, and E. S. R. 38 mm.

Physical therapy consisted initially of infrared therapy, with subsequent passive exercises through the normal range of motion of the affected joints. The left shoulder joint became free of pain after three weeks treatment with antibacterial chemotherapy and exercise, but remained stiff until the fifth week. The left ankle joint gradually improved and became asymptomatic after three weeks' therapy. The right knee became negative after four weeks' therapy. Active range of motion was initiated after 14 days of therapy. The patient ambulated during the fifth week of therapy. She recovered without sequelae and was discharged at the conclusion of five weeks' therapy, to be followed in the outpatient department, where she has continued to do well for three months.

Comment

H. influenzae remains high on the list of dangerous micro-organisms in infants, owing to its dual role as a primary pyogenic agent responsible for diverse clinical conditions and as a secondary invader in virus influenza. A higher incidence of H. influenzae bacteremia, pneumonia, and pyarthrosis would probably be revealed by the general use of early blood, sputum, and joint fluid aspiration cultures whenever the etiology is suspected.[27,28] Blood cultures of H. influenzae have required three to five days of incubation to become positive, owning to the fastidious growth of the micro-

organism.[28] Peterson,[6] and Weaver and Sherwood [15] emphasized that the prognosis for complete recovery in infants was good if the infection was localized to the joints, whereas that group of patients with complications, particularly meningitis, invariably died. It has been suggested [20] that since the advent of antibiotics localization in the bones and joints is less frequent and the prognosis less ominous. Human infection is for the most part limited to Type B H. influenzae, one of six distinct types.[29] The pathogenic potentialities of H. influenzae are dependent to some extent upon the host.[30] With advancing age, resistance to the organism increases, as shown by the bactericidal action of adult serum on the micro-organism.[31] Serum from infants over two months of age and young children lack this property. The joint involvement may be single or multiple and clinically indistinguishable from pyarthrosis caused by other micro-organisms. The diagnosis can be established only by identification of the micro-organism aspirated from the joint, and this should be done in all patients with acute suppurative arthritis so that adequate antibacterial treatment can be initiated before onset of complications. As in any patient with acute suppurative arthritis, three possible mechanisms [30] are responsible for the H. influenzae infection of the involved joint. The first is direct entrance of the micro-organism into the joint secondary to trauma; the second is hematogenous spread of the micro-organism, and the third is direct extension from neighboring areas of infection. The metastatic, or hematogenous, route is the most frequent and often occurs subsequent to pneumonia, upper respiratory infections, septicemia, meningitis, infected wounds, and furuncles. The possible explanation in our patient is hematogenous spread secondary to the upper respiratory infection which occurred prior to the onset of pyarthrosis.

Summary

The literature is reviewed, and a case is presented of acute suppurative arthritis due to Hemophilus influenzae, Type B, occurring in a 48-year-old Negro woman, who responded successfully to chemotherapy and recovered without sequelae.

3813 Garrison St., N. W. (16).

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CORRECTION

In the article "Studies in Myasthenia Gravis," by Dr. Kermit E. Osserman and colleagues in the July, 1958, issue of the ARCHIVES, a line of type was transposed in the first paragraph under "Symptomatology." The first two sentences of that paragraph should read: Table 1 summarizes all the initial symptoms present as well as all those that occurred subsequently during the course of the disease, although not necessarily present at one time. Fourteen per cent of the patients had subjective sensory complaints, such as nonspecific pain, cramps, headaches, and paresthesias."

Meprobamate Idiosyncrasy

Report of a Case and Review of the Literature

CAPT. N. DAVID CHARKES (MC), U. S. Army (Res.)

Meprobamate (Miltown, Equanil) was synthesized in 1950 by Ludwig and Piech in an effort to find a muscle relaxant with longer duration of action and fewer side-effects than mephenesin.[1] In the initial pharmacological evaluation, Berger discovered three unusual attributes of meprobamate which account in some part for its effectiveness as a tranquilizing agent, namely: (1) muscle relaxation due to selective blockage of interneuronal synapses but without effect on monosynaptic reflexes, impulse transmission in peripheral nerves, or activity at the neuromuscular junction; (2) peculiar "taming" effect on monkeys in that aggression disappears, and (3) thalamic stimulation.[2] Although the drug has been in clinical use since 1954, reports of toxicity have been scattered, and only one review of adverse responses has appeared.[3] One death has been reported.[4] The purpose of this communication is to present a case of meprobamate idiosyncrasy with skin biopsy and skin testing, to review the published reports to date, and to discuss possible etiologic factors in the pathogenesis of the anaphylactoid reaction.

The records of more than 6500 patients have been summarized to date.[5-81] Twenty-three cases of attempted suicide,[6-19] and one hundred thirteen cases of idiosyncrasy have been reported.[18-68]

Adverse responses to drugs may be conveniently classified into five categories: (1) idiosyncrasy, (2) extension of a therapeutic effect, (3) allergic reaction, (4) poisonous effect, and, (5) intolerance.[82] In addition, one may consider habituation, tolerance, addiction, and withdrawal reactions.

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Adverse Responses

Idiosyncrasy.—Many new drugs astound patients and physicians alike by a dramatic but transient disturbance of homeostasis in the form of an anaphylactoid reaction following ingestion of only one or a few tablets for the first time. Meprobamate is no exception, since about one patient in 200 responds in this fashion, as in the following case report:

A 39-year-old white man who had been taking promazine for six weeks without striking benefit because of insomnia, headache, jitteriness, and dyspnea, was instructed to take meprobamate, 400 mg. four times daily, on Sept. 4, 1957. Physical examination at this time was within normal limits save for tachycardia with a rate of 100 per minute and known labile hypertension with pressures as high as 138/104. A complete blood count one week previously revealed 7000 white blood cells per cubic millimeter, with 57% polymorphonuclear leukocytes, 2% band forms, 35% lymphocytes, 3% monocytes, and 3% eosinophils; the erythrocyte sedimentation rate was 11 mm. in one hour (Wintrobe); hematocrit 46%; hemoglobin 14.4 gm. per 100 ml.; total protein 7.72 gm. %, with albumin 4.17 gm. % and globulin 3.55 gm. %. An electrocardiogram was normal, as was a standard posteroanterior roentgenogram of the chest. Approximately three hours after ingestion of his first tablet of meprobamate, the patient developed a burning sensation of the forearms and axillary aching. He returned immediately to the clinic and was seen by another physician, who found an erythematous rash of the forearms and urticarial eruptions on the buttocks. The patient was advised to discontinue meprobamate and was begun on chlorpheniramine (Chlor-Trimeton) maleate, 4 mg. orally every four hours, which he continued to take for the next five days. Returning home, he experienced severe headache, a burning sensation all over his body, diffuse arthralgias, especially

of the wrists and elbows, nausea, vomiting, and severe low-back pain. Approximately six hours after the onset of the drug reaction he had several shaking chills and his oral temperature reached 102 F. Shortly thereafter he noted a rash "like the measles" on his arms, trunk, and buttocks and had difficulty in sleeping during the night because of the burning sensation and joint and muscle pains.

When seen in the clinic the next morning, however, he did not appear to be acutely ill. His temperature was 98 F orally, pulse 100 a minute, and blood pressure 130/95. The skin was cool and dry except on the inner aspect of the arms and forearms, the chest, the buttocks, and the inner surface of the thighs, where there was a warm, erythematous blush which blanched on pressure. There were moderate nonpitting edema of the forearms, neck, and wrists, axillary tenderness without palpable lymph nodes, hyperplastic and hyperemic lymphoid tissue of the pharynx, and a markedly positive Rumpel-Leede test. Physical examination was otherwise unremarkable.

The white blood cell count was 11,650 per cubic millimeter, with 62% polymorphonuclear leukocytes, 20% band forms, 14% lymphocytes, 1% monocytes, and 3% eosinophils. Red blood cells numbered 5,830,000 per cubic millimeter, hematocrit 49%, hemoglobin 16.2 gm. per 100 ml., erythrocyte sedimentation rate 12 mm. in one hour (Wintrobe), bleeding time 1 minute 35 seconds (Duke-Ivy), clotting time 9 minutes 35 seconds (Lee-White), platelets 326,480 per cubic millimeter, total protein 6.90 gm. %, albumin 3.66 gm. %, and globulin 3.24 gm. %. Urinalysis was negative save for a trace of albumin. Repeat chest film showed no change from the normal roentgenogram taken previously. The patient stated that he had had no drug reactions before and denied having hay fever, asthma, or urticaria. He had never taken mephenesin previously, to his knowledge.

He continued to have a headache and back pain throughout the day, as well as chilly sensations and discomfort in the back of his neck. The following morning the erythema had markedly regressed, but there were many small petechiae in the areas where the rash had been. Nonpitting edema of the neck posteriorly and of the posterior aspect of the thighs was prominent. A biopsy specimen was taken of the skin of the hip, where a faint blush was still discernible, and a few petechiae could be seen. The microscopic description was as follows (Fig. 1):

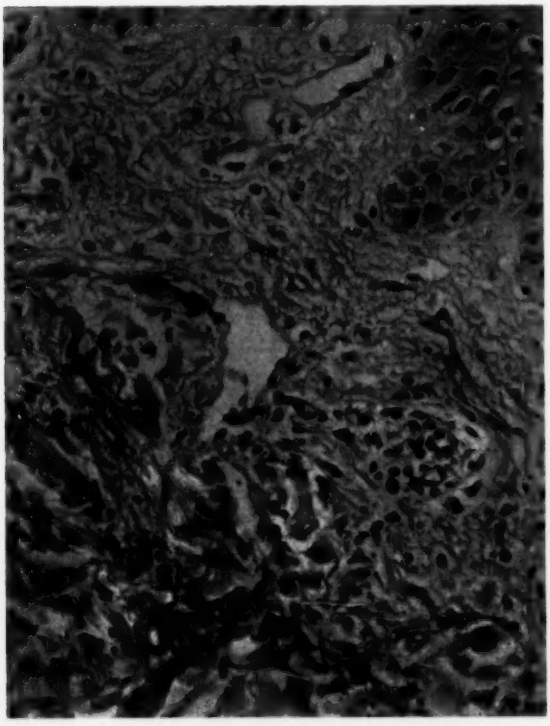

Fig. 1.—Note the dilated capillaries, lymphatics, and venules, and the perivascular infiltration of round cells. The upper part of the dermis is edematous. × 450. U. S. Army Photograph.

"There is slight hyperkeratosis and plugging of the hair follicles. Occasionally the epidermis is infiltrated with acute and chronic inflammatory cells, with a disruption of the basal layer and spongiosis. The principal alteration is situated in the dermis proper. There are subepidermal edema and nonspecific vascular reaction, which is mainly confined to the upper dermis. This vascular response is characterized by prominent and dilated capillaries, venules, and lymphatics, by perivascular edema, and by a moderately severe perivascular infiltrate of predominantly chronic inflammatory cells, as well as a few segmented leukocytes, some of which are eosinophils. Mast cells are inconspicuous."

During the succeeding week the patient noted occasional transient burning and erythema of the thighs. Complete physical examination five days after the onset of the adverse reaction was negative. Laboratory studies at this time revealed a white blood cell count of 6400 per cubic millimeter, with 47% polymorphonuclear leukocytes, 9% band forms, 40% lymphocytes, and 4% eosinophils; a red blood cell count of 4,890,000 per cubic millimeter; hematocrit 45%; hemoglobin 15.0 gm. per 100 ml.; erythrocyte sedimentation rate 16 mm. in one hour (Wintrobe); bleeding time 3 minutes (Duke-Ivy); clotting time 8 minutes 29 seconds (Lee-White), and platelets 215,120 per cubic millimeter.

One month later scratch tests with meprobamate alone and meprobamate incubated for one hour at 37 C with a preillness serum were both negative. He was given a trial with mephenesin, 500 mg. four times daily for two days, with subsequent "tightness" in his chest, dyspnea, hyperperistalsis, itching of the neck and shoulders, and drowsiness. Sera which had been obtained 6 days prior to and 18 hours following ingestion of the meprobamate tablet, and thereafter stored at 4 C, were injected intracutaneously, 0.1 ml. of each. The former produced an immediate wheal 11 mm. in greatest diameter, a flare, and mild burning; but the latter resulted in a wheal 18 mm. in greatest diameter, a greater flare, and a marked burning sensation, "just like I had all over me when I took the Equanil."

In one-third of the 113 cases of idiosyncrasy reported, the reaction began within eight hours of commencement of drug therapy, and all reactions had occurred by the end of the first week, except in 2. The earliest response was within 15 minutes. In no case had the reaction been seen in a suicidal attempt, so that excessive dosage was not a factor in precipitating it. The rash was erythematous, maculopapular, or urticarial, or a combination of these, as in the case reported herein, and may resemble a "boiled lobster."[20] Vesicular and pustular eruptions have been noted occasionally.[21-23] The rash was most prominent in the groins, inner thighs, buttocks, chest, axillae, and the antecubital and inframammary folds; fixed eruptions have been seen.[24] Petechiae were noted in 16%, almost always nonthrombocytopenic. Ecchymoses were rare, and the only patient with overt bleeding had aplastic anemia.[4] The Rumpel-Leede test of capillary fragility was always positive in cases of purpura. A prominent, and often distressing, symptom in one-fifth of the cases was pruritus; however, many patients complained only of "burning" or a sensation of warmth.

Other symptoms included anorexia, nausea, vomiting, diarrhea, yawning, headaches, chills, and fever, with temperatures of 101 to 103 F. Dizziness, fainting, hypotension, or shock occurred in almost 15%, and a few patients reacted with asthma, ectopic cardiac rhythms, numbness of the legs, emotional upsets, or mental confusion. A prior history of drug or pollen allergy was elicited in only a small number of patients but, whereas the anaphylactoid reaction rate was only 0.5% for the group of 6500 as a whole, it was 10 times as great in patients with known allergies.[25] Three of the cases of hypotension occurred in hypertensive or arteriosclerotic persons in their sixth or seventh decade,[26] although in clinical trials the drug exhibited little, if any, effect on lowering elevated pressures.[27,28]

Urinalysis, even in cases of purpura, was routinely negative except for three cases of transient, mild albuminuria and microscopic hematuria.[29-31] In about half the cases there was a mild polymorphonuclear leukocytosis with counts up to 22,000 cells per cubic millimeter, associated with and preceded by an absolute lymphopenia. Eosinophils accounted for less than 6% of the total white cell count. The rise in hemoglobin, hematocrit, and red blood cell

count, concomitant with an 11% decrease in the total protein content of the serum and microscopic edema of the dermis, described in the case reported herein, has not been noted before. It is characteristic of the exudation of protein-rich fluid through damaged capillaries, as has been described after intra-arterial injection of histamine.[83] The bleeding time, prothrombin time, and clot-retraction time have been within normal range, but in two out of nine cases the Lee-White clotting time was slightly prolonged, to 14 minutes.

The duration of the reaction varied from less than 1 day to 1 week, with an average of 48 to 72 hours, except for the fatality due to aplastic anemia. Most patients were treated with antihistaminics; in no case was relief dramatic, and in five cases, including the one reported herein, the eruption proceeded during the course of their administration. Steroids have been useful in the management of the severer reactions, such as those in which shock had occurred,[32,33] but it seems doubtful that their employment in the milder varieties contributes much to the well-being of the patient. It is well to point out that in one instance hypotension was of the orthostatic type and was relieved by the prone position.[34] The most effective step in the management of the patient was the cessation of meprobamate therapy. Epinephrine was administered in one case, with no effect on the course of the reaction.[34]

Many investigators attempted to prove conclusively that the reaction was due solely to meprobamate by the administration of one tablet (400 mg.) some time later. This is a dangerous practice and should not be attempted merely to satisfy the curiosity of the clinician. Twenty-eight of thirty patients who were given another tablet responded with a reaction which was frequently more violent than the original, and which in several cases was accompanied by severe shock. At best, this second reaction lasted longer and responded more slowly to steroid therapy than the first one. Several physicians tried readministration of one-fourth or one-half a tablet; the patient not infrequently disobeyed instructions and took the whole tablet, with dire results.

Unfortunately, there is no simple clinical test to determine beforehand which person is idiosyncratic toward meprobamate. Of the eight reported skin tests (patch or scratch) with the drug, six were completely negative, and two produced mild pruritus at the site but no objective findings. Passive-transfer tests were also negative in four patients.[30,31] Likewise, a scratch test using meprobamate which had been incubated with the patient's serum was also negative.

A fatal case of aplastic anemia has occurred, involving a 28-year-old woman who took 24 tablets (9.6 gm.) over an eight-day period and died seven weeks later, after intensive therapy with steroid hormones, antibiotics, and blood transfusions. Bone-marrow aspiration during life and after death revealed severe hypoplasia of all myeloid elements, with only occasional mature lymphocytes.[4] Chronic toxicity studies in a small number of dogs and rats have shown no adverse hematologic or renal effects.[2]

Other idiosyncratic responses to meprobamate which have been reported as isolated symptoms include diplopia, diarrhea, excitement, sneezing, and exhaustion.

Extension of Therapeutic Effect.—Twenty-three suicide attempts have been made [6,19] with up to 100 tablets (40 gm.), but there have been no deaths. Depression of the sensorium occurred with regularity and varied from a state of somnolence, in which the patient was rousable, to deep coma. There was little correlation between dosage and state of depression, coma having been reported with as few as 15 tablets (6 gm.) [6] and only marked drowsiness with as many as 56 tablets (22.4 gm.).[7] Deep tendon reflexes were usually markedly diminished and frequently completely absent; there was often no response to pain. In a few cases complete flaccidity of the extremities was noted.[6,8,9] This exaggerated degree of mus-

cular relaxation is due to the blockade of interneuronal synapses within the central nervous system. The pupils were either dilated or constricted to pinpoints, were slightly reactive or nonreactive to light, and the gaze occasionally wandered aimlessly. The corneal reflex was absent in the one case in which it was mentioned. Occasional patients vomited or were cyanotic; airway obstruction occurred. In the majority of cases the blood pressure was low; occasionally patients were in shock, with rapid, thready pulse. Respirations were usually shallow, but regular, and less than 28 per minute. A mild leukocytosis and neutrophilia were not uncommon, but studies of urine and hepatic function were normal. In one patient, who took 90 to 95 tablets, the urine for the first 24 hours had a "peculiar pungent, fruity odor," said to be similar to the odor of meprobamate itself [9] (10% of the drug is excreted unchanged in the urine during the first 24 hours.[2]) In two cases subnormal temperatures were noted: One patient seemed to be in a state of hibernation.[8] This may represent an extension of the antipyretic action of meprobamate.[2] Recovery occurred in from 4 to 72 hours, and after-effects of tinnitus, dizziness, nausea, or agitation, which occurred in a few patients, were minimal. Therapy usually included gastric lavage, parenteral stimulants, clearing of the airway, intravenous fluids, hypertensive agents when indicated, and penicillin occasionally. In two cases [10,11] picrotoxin roused the patient rapidly, but had no apparent effect on the total duration of intoxication. Similarly, pentylenetetrazol (Metrazol) has been reported to produce rapid return of consciousness and reflexes but is ineffective in relieving hypotension [8] (meprobamate prevents Metrazol-induced convulsions in mice [12]). One person who became comatose after ingesting 50 tablets recovered in three days without benefit of a physician's attendance.[13]

In addition to the effects of marked overdose, many side-effects attributable to therapeutic dosages and extensions of them have been mentioned. Drowsiness and fatigue are quite common, especially at higher dosage levels, but tend to wear off without change in dosage in days or, at most, weeks. Neurologic manifestations may include tremor, incoordination, ataxia, dysarthria, and euphoria, and a state of resembling drunkenness has been described by a number of authors.[14,23,66] Mild nausea was described in 10% of one large series and constipation in 17%, but vomiting, abdominal discomfort, cramps, and diarrhea are uncommon. Barium studies of the stomach and intestine have been normal.[14] Electroencephalographic changes, consisting of fast activity over the frontal areas, were reported by one group [67] but not by another.[37]

Intolerance.—Sensitivity to therapeutic doses has been mentioned in the literature, particularly neurologic manifestations. One patient became comatose after ingestion of only 8 tablets daily for two weeks,[38] and six others exhibited dyskinesias on relatively moderate amounts of the drug.[39] Reactivation of ulcer symptoms has occasionally been seen.[40-42]

Poisoning.—The only side-effect which seems to be an almost universal phenomenon following ingestion of large amounts of meprobamate, and unexplained at present by known mechanisms, is hypotension. Intravenous administration of 40 mg. per kilogram to cats produced a fall in blood pressure of 25-40 mm. Hg,[2] but when injected intramuscularly in the cat and taken orally in man,[27,28] there is little, if any, effect at therapeutic dosages.

Allergic Reactions.—True hypersensitization states due to meprobamate are rare, and have taken the form of erythema multiforme in four of the five cases.[24,33,43] A "waiting period" of two weeks to four months separates this group of reactions sharply from the idiosyncrasies, which have all occurred within seven days of commencement of therapy. However, the other manifestations of the reaction are the same, including the appearance of shock on rechallenge. Two of the cases lasted for more

than a week, and required steroid therapy. A skin biopsy revealed capillary dilatation and perivascular round-cell infiltration.[19]

Habituation and Withdrawal.—Early reports indicated that meprobamate did not produce addiction; since then the true capacity of the drug has become known. Lemere[44] described six patients addicted to ethanol and barbiturates who stopped taking meprobamate because they felt they were "getting hooked" (i. e., addicted), and Phillips, Judy, and Judy[38] reported two patients with withdrawal symptoms, one of whom also had developed a tolerance to the drug. Seven patients have since been described who complained of anxiety, insomnia, headaches, weakness, nausea, and salivation following abrupt cessation of meprobamate therapy[45-47]; in the two patients on whom electroencephalograms were obtained, a transient mixed dysrhythmia was found. Lemere has also noted the development of drug tolerance by nine patients.[44]

Seizures following abrupt withdrawal from up to 6.4 gm. of meprobamate daily (16 tablets) were reported in six patients who had never had convulsions before.[44, 46-49] It has been demonstrated in mice that following sudden cessation of high-dose therapy there is a transient decrease in the electroshock threshold,[84] and four dogs given more than 8 gm. daily of meprobamate for six months became markedly restless following abrupt withdrawal, rapidly developing marked motor hyperactivity, culminating in convulsions. Three of the dogs died after repeated seizures.[47]

It would seem desirable to taper off large doses of the drug over a period of days rather than stop therapy abruptly.

Comment

The occurrence of a generalized burning sensation, urticaria, erythema, vomiting, fever, nonpitting edema, arthralgias, adenopathy, and petechiae in the subject of this case report, as well as hypotension, pruritus, bronchospasm, hyperperistalsis, headache, and disturbed sensorium in other patients

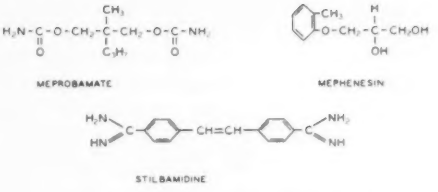

Fig. 2.—(U. S. Army Photograph)

reported in the literature, immediately brings to mind the possibility of a drug allergy. However, there are several factors which militate against this. First of all, the patient in this case report reacted to his first and only tablet of meprobamate within three hours of ingestion, and two-thirds of the 113 patients in the literature to date did so within 48 hours of commencement of therapy. It is well known that in one common form of true hypersensitization state, serum sickness, an incubation period of 7 to 10 days is almost always the rule[82]; only five patients fell into this category. In order to account for this extremely rapid reaction to a new drug, it might be postulated that at some time in the past the patient was sensitized to a drug of similar chemical configuration, such as mephenesin (Fig. 2). To test this hypothesis, the patient was given a total of 4.0 gm. of mephenesin over a 48-hour period, 4 weeks after his meprobamate reaction. He experienced very mild bronchospasm, hyperperistalsis, drowsiness, and pruritus. Symptoms were most marked shortly after ingestion of the drug. He had never had this combination of symptoms before in his life and had never taken mephenesin to his knowledge. No patient with an anaphylactoid response to meprobamate has yet been reported who previously had an untoward reaction to mephenesin.

Unfortunately, skin testing is of almost no value in settling the question, since even in truly allergic dermatitis medicamentosa skin tests are almost always uniformly negative and antibodies have never been demonstrated, although their existence is assumed for theoretical reasons.[82] Thus, a

negative scratch test, as in our patient and the patients reported, is of no help. Furthermore, a scratch test with meprobamate which had been incubated with a preillness serum was also negative. Nevertheless, the demonstration in the present case of histamine-like symptomatology associated with rising red blood cell count, hematocrit, and hemoglobin, an 11% decrease in plasma proteins, microscopic edema of the dermis, and a positive Rumpel-Leede test reproduce nicely the clinical and laboratory findings demonstrable experimentally by intra-arterial injections of histamine in humans.[83]

Finally, the presence in the serum 18 hours after the onset of the reaction of a substance capable of producing greater whealing, flaring, and burning than a preillness control serum, is added evidence that in certain sensitive persons meprobamate may well be a histamine-liberating substance.

In summary, it seems very unlikely that the rapid development of an adverse reaction shortly after the institution of meprobamate therapy is due to true drug allergy; if such a mechanism is responsible, it is not demonstrable by current clinical methods, and cross sensitization to other agents, such as mephenesin, although theoretically possible, does not seem too convincing when tested clinically.

In recent years, however, it has become increasingly clear that the release of histamine can be effected not only by antigen-antibody reactions but also by numerous simple drugs, most of which are either basic amines, like meprobamate (Fig. 2) or surface-active agents. The problem has been recently reviewed thoroughly by Paton.[85] Among the more active compounds are straight-chained aliphatic diamines, diamidines (such as stilbamidine [4,4-stilbenedicarboxamidine]), diguanidines, diisothioureas, monoamines, monoamidines, basic amino acids (such as arginine), certain antibiotics and chemotherapeutic agents (such as polymyxin), centrally acting drugs (such as morphine), muscle relaxants (such as tubocurarine), amphetamine, and large-molecular compounds, such as dextran, horse serum, and ovalbumin. These substances all possess the common characteristic of liberating histamine (and other agents, perhaps) when introduced into the body. For instance, the occurrence of hypotension, itching, diaphoresis, dyspnea, dizziness, nausea, epigastric discomfort, vomiting, syncope, incontinence of urine and feces, and puffiness of the face and eyelids following the intravenous injection of stilbamidine in humans is well known.[86]

One of the most widely studied drugs in this regard has been tubocurarine, the active principle of curare. When this is injected intra-arterially in the human forearm, there follows transient flaccidity, a burning sensation, objective warmth, ecchymoses, nonpitting edema, itching, wheal formation, an increase in volume of the arm distal to the site of injection, and, in a short while, giddiness, headache, and brief, mild hypotension.[87] All of these effects can also be produced by intra-arterial histamine, save for the flaccidity.[83] Larger doses of whole curare have resulted on occasion in severe shock with hemoconcentration; more moderate doses have produced bronchospasm, salivation, marked increase in gastric acidity, and urticaria.[87,88] Furthermore, intracutaneous tubocurarine (or curare) produces an immediate wheal and flare, which is completely preventable by prior preparation with antihistaminics locally, or in large amounts by mouth. Reactivity is proportional to histamine sensitivity. Tubocurarine also produces a measurable increase in circulating histamine in the dog in vivo and releases histamine from the guinea pig lung.[89] In addition, this compound causes disintegration of mast cells, which are a potent source of tissue histamine.[90] This latter phenomenon has been studied by Riley, principally with the active diamidine histamine liberator, stilbamidine.[90] He has found that this substance, as well as several other histamine liberators, including tubocurarine, is taken up by the perivascular mast cells, with re-

sulting disruption of the morphology of the cell, particularly the characteristic granules, followed by local vascular dilation and edema. Antihistaminics administered prior to stilbamidine totally inhibit the vessel response but do not prevent the mast cells from absorbing the diamidine. However, in the rat, edema following the injection of histamine liberators seems to be due mostly to the release of 5-hydroxytryptamine.[85] Studies on the ability of meprobamate to lyse mast cells would be most helpful in resolving this question.

Some comment is needed on the somewhat prolonged clotting time reported in two of the nine cases in the literature. In the dog, injection of various histamine liberators causes incoagulability of the blood, attributed to increased amounts of circulating heparin. Since heparin, as well as histamine, is present in the granules of mast cells,[85] it is tempting to speculate upon the ability of meprobamate to release it in certain sensitive persons.

Summary

Reports concerning over 6500 patients treated with meprobamate, including 23 attempted suicides and 113 anaphylactoid reactions, with 1 death, are reviewed, and a case of idiosyncrasy is presented. There is no way of knowing before hand which person will react adversely (1 in 200 does), except that allergic persons are 10 times as likely as normals to do so. The most important step in management of the anaphylactoid reaction is discontinuation of meprobamate; rechallenge by an oral dose is dangerous and should be discouraged. Indirect evidence is adduced implicating meprobamate as a histamine-liberating agent in certain patients.

Lieut. Col. Helmuth Sprintz interpreted the microscopic sections.

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Treatment in Internal Medicine

The physician charged with the management of the patient with peptic ulcer always faces the difficult task of choosing the course of action which is most likely to work for the patient under consideration, regardless of theoretical considerations. Such factors as the patient's occupation, financial status, and temperament must inevitably influence the choice of management. In the two papers which follow, a gastroenterologist of wide experience gives a sound evaluation of the internist's approach. A surgeon, equally familiar with the field, gives the pros and cons of the various surgical procedures now available. While every question in connection with treatment of peptic ulcer patients is not answered, it is unlikely that any more practical coverage of the over-all problem can be found.

PAUL S. RHOADS, M.D., Chief Editor

The Medical Management of Peptic Ulcer

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The problem of peptic ulcer is important in the general economy if only by virtue of the fact that 5% to 10% of the population of this country at some time during their lives will have such a lesion. Fortunately, most of these persons do not experience any serious consequence of the disease, and many have little difficulty in controlling its symptoms. However, the morbidity produced by a disease of this magnitude of occurrence makes its recognition vital and calls for intelligent appreciation of the essentials of treatment that render control of the lesion a reasonable possibility.

Were the cause of peptic ulcer more accurately understood, it is likely that its treatment would be more efficacious and less diverse. In a broad sense, two major schools of thought exist with respect to the treatment of ulcer; the first emphasizes a strict ritual of diet, antacid medicines, sedatives, and anticholinergic drugs, whereas the second emphasizes the psychotherapeutic aspects of the problem at the expense of all else. Actually, as long as the cause of peptic ulcer is unknown, it would be unwise to assume too rigid an approach to its treatment, because both these concepts contain an element of truth that can give promise of aid when they are honestly and intelligently applied.

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Pathophysiology of Peptic Ulcer

As already intimated, the concept of the etiologic factors in peptic ulcer is diverse. Trauma, focal infection, vascular lesions, nutritional deficiencies, tissue susceptibility, excessive secretion of acids, allergy, and psychosomatic factors are some of the causes that have been suggested. The presence of free hydrochloric acid in the gastric juice is a prime feature of peptic ulcer. The formation of ulcers and the major symptoms of these lesions depend greatly on this factor of acidity. The very name of the lesion is a concession to the thesis that a major cause is the corrosive action of a proteolytic enzyme known to be dependent on free hydrochloric acid for its activation. Having accepted this position, one is immediately confronted by new problems, not the least of which is to explain why ulceration does not occur in every stomach or duodenum. One explanation given for the genesis of ulcer is a disturbance of the normal balance between the aggression of acid and the tissue defense. It becomes less easy to explain in a logical and convincing way

what these factors really represent, and no satisfactory method is as yet available to control them.

The fact that acid plays an important role in the cause of ulcer necessitates at least some understanding of the factors that control the output of acid. Secretion of acid in some animals appears to be continuous, even in the absence of specific stimuli. Whether the secretion of acid in man is continuous is less clear. Studies of nocturnal secretion suggest that gastric secretion in certain circumstances may be continuous. However, the output of acid is variable when normal persons are compared with patients having certain diseases, such as duodenal ulcer, and evidence exists that under normal conditions the output of acid is not necessarily continuous.

The normal basal secretion in man is affected by appropriate stimuli that are classifiable into three broad categories, namely, the cephalic phase, the gastric phase, and the intestinal phase.

Cephalic Phase.—This is the initial stimulus to gastric secretion and is mediated by the vagus pathways. The importance of this phase can be quantitated by the effect of insulin-induced hypoglycemia, which is believed to stimulate the vagus center in the brain and which is well known as a potent stimulus to the production of gastric acid. The mediation via the vagus nerves of a stimulus to the output of gastric acid arising in the brain lends physiologic credence to the suggested etiologic role of nerve tension and other psychic stimuli in producing hyperacidity and, secondarily, peptic ulcer.

Gastric Phase.—This phase in the output of acid is most important. Oral ingestion of food initiates the output of acid in the intact stomach. The stimulus that produces this effect is apparently, in part at least, hormonal in its character, since the response occurs even after complete denervation of the stomach.

Intestinal Phase.—This phase of gastric secretion is less well understood. Serious doubt exists that food in the intestine of itself actually is a stimulus to gastric secretion. The presence of depressants of gastric secretion produced by the intestine is better documented. Fat in the duodenum and upper portion of the small intestine inhibits the gastric secretion elicited by food. This effect has been thought to be caused by a hormone called "enterogastrone," whose isolation led to a hope that it would offer a clinical means of controlling gastric secretion in patients with peptic ulcer. Unfortunately, this hope has not materialized.

The relationship of free acid to the development of peptic ulcer has long been accepted. An important relationship undoubtedly also exists between gastric acidity and the pain of ulcer. Some authors consider that gastric acidity is the primary factor in ulcer pain,[1] whereas others think that much of the distress caused by ulcer can be related to motor activity of the stomach and duodenum.[2] The pain of ulcer undoubtedly results from a combination of factors that encompass the effect of free acid on the ulcer itself, motility, and the inflammatory reaction that is associated with the ulcer. Clinical experience indicates that alleviation of pain in and healing of peptic ulcer depend to a large extent on the control of free acid. The relief of pain is an excellent sign of the effectiveness of control of gastric acidity; persistent pain may reflect ineffective neutralization of acid, although it also may be due to other factors, such as the inflammatory reaction incident to subacute penetration of the lesion.

Justification for Medical Treatment of Peptic Ulcer

The incidence of the lesion is in itself justification for a serious consideration of the principles of therapy. A lesion that affects 10% of the total population certainly is an important one. Some observers have suggested that peptic ulcer should be treated medically except in patients with the se-

verest complications. Others have intimated that the lesion should be treated largely by surgical means. Somewhere between these two extremes lies the truth. It is fortunate that the vast majority of patients with duodenal ulcer are able to achieve healing of the lesion and freedom from symptoms with only minor restrictions in their habits of living and eating. For some years at the Mayo Clinic, surgical treatment has been required for only about 15% of all patients in whom a diagnosis of duodenal ulcer has been made. The situation is somewhat different in gastric ulcer, with surgical intervention occurring in 60% to 70% of such lesions diagnosed. A major reason for this is the ever-present possibility of malignancy in gastric lesions, a problem that can be resolved most effectively by excision of the lesion. Nonetheless, a majority of small circumscribed gastric ulcers are benign peptic ulcers, many of which will heal promptly with adequate medical care.

Choice and Method of Treatment

The classic concepts of the treatment of peptic ulcer of the stomach and duodenum promulgated by Sippy[3] still form the bulwark of the most successful management of these lesions. Sippy emphasized prolonged neutralization of acid under controlled conditions, with use of a properly modified diet and adequate administration of antacids. The diet was bland, avoiding mechanical and thermal factors and excluding any food thought to be a secretagogue. Antacids were given in sufficient quantity to achieve continuous neutralization of acid. Sippy's basic concepts unquestionably have stood the test of time; if carefully applied, they still give the best hope for control of ulcer from the medical standpoint. Time has shown, of course, that modification of Sippy's methods is essential to avoid the hazard that attends prolonged use of absorbable alkalies and large quantities of milk.

Although Sippy's original observations were recorded on hospitalized patients, his principles can be applied equally well to ambulatory persons. Under ordinary circumstances, hospitalization is reserved for the patient whose problem is difficult, ambulant care usually being sufficient for the average patient. When factors of emotional stress are important, a period of treatment in a hospital environment may be of much help. Without question, many ulcer patients are greatly benefited by an initial period of hospital treatment for control of symptoms and adequate instructions in subsequent care.

Sippy originally stressed the importance of complete neutralization of free acid as a greatly desired goal in therapy. In practice, it is exceedingly difficult to accomplish complete neutralization throughout a 24-hour period, and, furthermore, it has been shown that constant complete neutralization of gastric acidity is not necessary to achieve healing of an ulcer. Apparently, a reasonable reduction in gastric acidity allows for sufficient modification of destruction and repair of tissue to permit ulcer healing. During the early years of the Sippy regimen, absorbable alkalies were employed freely to achieve neutralization of acid. As early as 1923,[4] attention was called to the inherent danger of the overuse of these substances; subsequently, nonabsorbable antacids have been developed that, although chemically less effective in vitro, afford a practical means of effective reduction of gastric acidity at no risk to the patient.

Milk has long been the sheet anchor of the medical regimen in ulcer. It has been recognized with increasing frequency during recent years[5-7] that excessive use of this food, particularly when combined with absorbable alkalies, can cause hypercalcemia, which can lead to secondary renal damage. Increasing awareness of the possible relationship of degenerative vascular lesions to high intake of fat has cast further suspicion on the mixtures of milk and cream formerly used so freely in the medical management of ulcer. The inherent

weaknesses of the Sippy regimen as it was originally conceived have been recognized; despite this, it is perhaps an indictment of the medical profession's lack of understanding of peptic ulcer to observe that the general principles of the Sippy regimen, with modifications, still form the backbone of the medical approach to the problem of peptic ulcer.

Principles of Treatment

Rest.—This principle, although often neglected, is essential in the adequate treatment of peptic ulcer. The efficacy of hospitalization in controlling ulcer symptoms often rests less in the realm of the adequate dietary and medicinal program possible in such surroundings and more in the realm of the physical and emotional rest that this environment affords the patient. The importance of psychosomatic factors in the genesis of peptic ulcer and its reactivation is well recognized by all students of the disease. These are factors of paramount importance in many patients. Ulcer patients are characteristically hypersensitive, overworked, and worrisome and are often exposed to serious emotional stress either at their places of business or in their homes. Many patients volunteer that exacerbations of ulcer distress are brought under prompt and complete control by the simple expedient of escape from the corrosive effects of these stress factors, sometimes by a vacation, without modifying ordinary dietary habits or attempting medicinal control of gastric acidity. This observation is made so frequently that its significance must not be ignored, nor can the lesson to be learned be overemphasized.

Modification of living and work habits in patients in whom factors of physical stress and overwork are apparent is essential to control of the lesion, both in the immediate period of healing and in the interval phase when reactivation of symptoms is to be avoided. Control and elimination of emotional stress are equally desirable. This is usually possible on a simple supportive basis and can be accomplished best by the internist in charge. Emotional factors sometimes become so involved as to necessitate psychiatric help. Under such circumstances, the aid of a psychiatrist should be promptly enlisted.

Experience indicates that emotional and physical stress presents the most formidable problems of all the factors that need to be controlled in the treatment of peptic ulcer, since the patient so often is either unwilling or unable to make the adjustment necessary to control such stress.

Diet.—The factor of diet in the management of ulcer is important. To many persons, dietary modification in some degree constitutes ulcer therapy. A subtle danger lurks in this attitude, one that leads to disdain of other equally important factors and one that, if maintained, foredooms the treatment to failure.

Sippy emphasized use of a diet that avoids mechanical, chemical, and thermal stimuli to the production of acid. These principles still motivate the physician's advice to the patient. From the practical standpoint, it is rare that the diet need be restricted to hourly feedings of milk only. A satisfactory diet for the patient who has an active ulcer consists of three feedings of bland foods, excluding meat, with hourly feedings of 4 fluidounces (120 ml.) of whole milk, starting at 7 a. m. and continuing to 9 p. m. Such a diet is nutritious and adequate in calories; it avoids an excess of milk and excludes foods that offer a stimulus to the production of acid. This diet rarely need be continued for longer than one month. Once the ulcer symptoms are under control and it is deemed that healing of the lesion is progressing satisfactorily, the diet can be advanced to three meals consisting of bland foods and properly prepared meat, with three daily feedings of 8 fluidounces (240 ml.) of milk (one at midmorning, one at midafternoon, and one at bedtime). Such a diet is well balanced and palatable, can be continued indefinitely, and is adequate except for a minor lack of

vitamins, which can be supplied by one hexavitamin capsule, U. S. P., taken daily. This dietary regimen has the virtue of simplicity, which is desirable if it is to be continued for a prolonged period. No efficacy has accrued to unusual dietary measures.

Antacids.—The choice of antacid therapy often poses a problem to the physician. The antacids originally employed by Sippy unquestionably were efficient in the neutralization of acid. As already indicated, these antacids contained large quantities of absorbable alkali that, in the quantities necessary, led to disturbing toxic manifestations in some cases. It soon became evident that an antacid was needed that was an efficient neutralizer of acid and yet nontoxic with prolonged use.

Theoretically, an ideal antacid is one that is palatable; unattended by untoward reactions, such as alterations in acid-base equilibrium; possessed of prolonged neutralizing effect when given in small quantities; unattended by a secondary increase in gastric secretion, and low in cost. Unfortunately, such an ideal antacid is still to be found.

Modification of antacid therapy made necessary by recognition of the baneful effects of excessive use of absorbable alkalies has led to the widespread administration of preparations of aluminum hydroxide. This substance possesses a theoretic neutralizing effect greater than that of calcium carbonate, long recognized as an extremely efficient and satisfactory antacid. To be effective, aluminum hydroxide must be used in large doses; it has two objectionable features in that it tends to increase the excretion of phosphate in the urine and has a pronounced constipating effect. A judicious combination of aluminum hydroxide with the trisilicate or hydroxide forms of magnesium has resulted in a satisfactory antacid that is clinically efficient as a neutralizer of acid, safe when given in large quantities for prolonged periods, and free from troublesome constipating effects. These preparations as currently available undoubtedly will continue to enjoy extensive application until a clearly superior antacid is available. Of the many other antacids introduced, one can mention mucin, orally administered protein hydrolysates, anion-exchange resins, and detergents. None of these has been shown to possess virtues that would warrant its preference to the aforementioned mixtures of aluminum hydroxide and magnesium salts. The latter preparations are available in liquid or tablet form. Patients often prefer the tablet because of its ease of handling. However, the liquid preparation is to be preferred and used whenever possible, since it possesses a more effective antacid effect than does the tablet.

In practice, antacids are given at hourly intervals during the day, during the active phase of ulcer therapy. In patients who have severe symptoms, nighttime administration of antacids at intervals of two hours with small amounts, such as 4 fluidounces, of whole milk is exceedingly helpful and maintains control of gastric acidity during the interdigestive phase; failure to recognize the importance of such control during this phase often defeats the success of what would otherwise be an entirely adequate regimen. When ulcer symptoms are under control and the lesion is considered to be healed, the use of antacids can be reduced to approximately six times daily, with administration at intervals of one and one-half hours prior to and following each meal and at bedtime; it is not necessary, of course, to give a dose before breakfast.

Antisecretory and Motor-Inhibitory Drugs.—Although it can be reasonably maintained that use of antacid drugs has been an incalculable boon in the control of gastric acidity and thereby the healing of duodenal and gastric ulcers, yet it is true that a more physiologic approach would be to prevent the formation of acid rather than to neutralize it when once produced. This concept was well expressed in the

hopeful prediction of Kirsner and associates,[8] "The continued exploration of hormonal factors, of drugs acting upon enzyme systems possibly implicated in the mechanism of gastric secretion, and the further development of cholinergic blocking agents may yet lead to the synthesis of a highly effective and safely administered compound for the sustained elimination of free acid in the stomach of man." These same authors went on to predict that such an accomplishment would provide the solution of the problem of peptic ulcer. Present knowledge of the lesion and experience in its treatment would appear to substantiate this hopeful outlook. It is less certain that the development of this ideal blocking agent is on the immediate horizon.

The inhibition of gastric acidity has been well documented in animals,[9] but the effective employment of this method in the human body is still awaited. The development of enterogastrone and urogastrone, hormone-like substances having a gastric secretory depressant activity in dogs, gave hope that at last a substance was available that would effectively suppress gastric acidity in man. Although these substances do suppress gastric secretion in dogs, no preparation of them is available that will produce the same effect in man when given by the intravenous route. When given subcutaneously or intramuscularly, their effect is unpredictable; when administered orally, these substances have no measurable clinical effect.[10]

Atropine and atropine-like drugs possess antisecretory and antimotility properties. Tincture of belladonna and atropine have a blocking effect on the parasympathetic postganglionic chemotransmitter mechanism. They definitely inhibit gastric secretion and gastrointestinal motility, as demonstrated by observations in both animals and man. However, these drugs possess an important disadvantage when given in effective doses because of their concomitant effect on parasympathetic chemotransmission in organs other than the stomach, such as the salivary gland.

New synthetic anticholinergic drugs now are available that, like atropine, are autonomic blocking agents. They have an antisecretory and antimotility effect, and their antisecretory action is more or less confined to the stomach; however, their antimotility action is not limited to the stomach. Typical of this class of drugs is methantheline (Banthine) bromide, which is a quaternary amine (β-diethylaminoethyl 9-xanthenecarboxylate methobromide). Methantheline bromide is a powerful inhibitor of gastric motility and possesses a definite antisecretory property when given in adequate dosage. Moreover, this drug and other similar agents have a sufficiently selective action on the gastrointestinal tract, so that their use as adjuvant agents in the control of peptic ulcer is recommended. Unfortunately, however, certain unpleasant side-effects attend the use of these drugs, and reasonable caution in their administration thus is advisable.

Sedatives.—The importance of rest in the treatment of peptic ulcer already has been emphasized. Since many ulcer patients are emotionally tense, some form of sedation is extremely useful and often essential. Phenobarbital is a safe, long-acting, inexpensive drug that can be most helpful to the ulcer patient, and many will benefit by the release of tension afforded by this drug during the active phase of the disease. Heavy sedation to the point of somnolence for a brief period by use of one of the barbiturates has been helpful on occasion in the control of severe ulcer distress in tense anxious persons in whom symptoms fail to respond to the usual measures of diet, physical rest, and control of gastric acids.

Roentgen Therapy in the Treatment of Ulcer

Certain ulcer patients are encountered in whom it is difficult or impossible to control the symptoms despite the most rigid adherence to the best principles of medical

therapy. A surgical procedure is usually necessary in these persons. However, surgical intervention may present a serious risk to some of these patients because of associated medical problems. In these instances, any more effective means for long-term control of gastric acidity would be welcomed.

Irradiation of the gastric region reduces all phases of gastric secretion, depending for its effect on the amount of irradiation administered and the tissue susceptibility of the patient. The duration of gastric anacidity thus induced is unpredictable and variable, but it may persist for prolonged periods. Ordinarily, the gastric mucosa eventually recovers its secretory function. Since irradiation of the gastric region by roentgen rays may effect achlorhydria of some duration, one can expect the method to afford a valuable aid in the control of ulcer symptoms and healing of an ulcer. That such is true is evident in well-documented reports,[11,12] which are encouraging, but further evaluation of this method of treatment is needed before its ultimate role in the management of peptic ulcer can be assigned. Certainly, the method does not supplant the usual principles of medical therapy, although it may prove to be a useful adjunct in difficult cases in which the lesion is refractory. Much more time must elapse before the safety of the method can be assessed because of the rather large amount of irradiation necessary and the unpredictable nature of the long-term effects of roentgen irradiation and its possible carcinogenic potential.

Prevention of Recurrence

If the patient with a duodenal ulcer can accept the fact that he should not speak of cure of his lesion but rather control of it, he will accept more readily the life-long cooperation that is essential in effective medical care of his ulcer. Although an acute duodenal ulcer, if adequately treated, may heal so completely as to leave no demonstrable radiologic deformity of the duodenum and no symptomatic recurrence of it may be evident for many years,[13] the natural history of the disease is one of exacerbation and remission. Careful analysis of the histories of patients with duodenal ulcer reveals that most such patients become careless of their habits during their asymptomatic periods, and one cannot escape the conviction that less likelihood of the recurrence would have been present had a more careful regimen been followed during the asymptomatic period. It is essential that the ulcer patient be aware that disappearance of his symptoms does not necessarily indicate complete healing of the ulcer. Effective neutralization of acidity usually results in prompt and complete control of symptoms, yet it is well known that the ulcer itself does not heal completely for many weeks. It is important, therefore, that any program of treatment be carefully maintained for a prolonged period.

It is usually desirable that the patient follow a strict regimen of therapy for at least four to six weeks after the initial control of active ulcer symptoms. Such a regimen presupposes that constant adequate control of acidity is achieved during the waking hours by ingestion of milk or bland foods at hourly intervals and the use of an effective antacid halfway between each feeding. In the early part of this period, control of acid during the nocturnal interdigestive phase may be desirable and can be accomplished by several feedings of milk or bland food in conjunction with a long-acting antacid, such as aluminum hydroxide gel. Once the symptoms have been under control for a month, vigilance can be relaxed somewhat. At this time, a full bland diet of three meals and intermeal and bedtime feedings of milk, with halving of the antacid program, should suffice. This program should be followed for at least a year. If the patient has remained asymptomatic during all this time, he can safely relax his regimen a little more. However, he should be impressed with the fact that he cannot now, or ever in the future, safely

ignore his ulcer, for to do so is to foredoom the medical treatment to failure. Rather, it is essential that the patient maintain constant vigilance to some degree. He should avoid assiduously all factors of stress and other habits that stimulate the output of gastric acids and never should depart entirely from moderate dietary restrictions for the rest of his life.

Unfortunately, the "ulcer personality" is such that few patients are willing to make the sacrifice necessary to follow a program of this kind for an indefinite period, but those who do usually are rewarded by good control of symptoms. The patient should be cautioned to exercise special vigilance during periods of unusual physical and emotional stress. It is also important that the patient understand that recurrence of ulcer should not be regarded lightly and that each episode can lead to further scar formation and ultimately some complication that cannot be resolved by conservative medical measures.

Gastric Ulcer—A Special Problem

Gastric ulcer continues to present a special problem because of the ever-present possibility that any ulceration of the stomach may be of a malignant character. Partly because of this and partly because of the low mortality rate associated with partial gastric resection for these lesions (less than 2%), a large proportion of patients with such lesions (approximately 60%) are treated by partial gastric resection at the clinic. However, since it is recognized that a majority of small circumscribed gastric ulcers which possess characteristics favoring benignancy will heal on medical treatment, there remains a considerable number of patients with gastric ulcer who will be treated medically. The decision to treat these patients medically may be motivated by desire on the part of the patient to avoid operation or may be a matter of expediency on the part of the physician because of associated medical problems that increase the surgical hazard beyond that of deferring operation for an unrecognized early malignant ulcer.

The findings of Cain and associates[14] present a powerful argument for partial gastric resection in a majority of cases of gastric ulcer. In that study, only 20.5% of 414 patients had satisfactory results from medical treatment and there was a high incidence of recurrent ulceration; approximately 10% of the lesions ultimately proved to be malignant. These authors concluded, ". . . the difficulties of applying the principles of good medical management and the ensuing unsatisfactory results of medical treatment invite early surgical intervention in a greater percentage of cases than at present." Smith and co-workers,[15] in a study of 1000 cases of a similar character, found an operative mortality rate of 4.85% in patients undergoing resection for benign ulcer and a mortality rate from gastric carcinoma in nonsurgical patients of only 1.7%. Furthermore, their study indicated that partial gastric resection does not necessarily protect the patient against the development of gastric carcinoma. These authors stated that a month or less of intensive medical management in many cases of gastric ulcer is justified.

The responsibility assumed by the physician in deciding on a course of medical treatment in any given case of gastric ulcer is great, recognizing that the most certain measure of the character of the lesion is its histologic classification. Healing of the lesion is of relative value only, since an occasional carcinomatous ulcer has been known to heal temporarily, as measured by all the usual roentgenographic and gastroscopic criteria of healing.

Before a decision is made to treat a gastric ulcer medically, the patient should be thoroughly acquainted with the problems presented. Responsibility for the outcome can be assumed by the physician only if the patient places himself without reservation under the physician's direction, agreeing to careful periodic examination of his stomach over an interval of 18 months or more if

the initial response is favorable, and understanding that partial gastric resection will be obligatory if satisfactory evidence of healing does not follow 3 or 4 weeks of careful medical treatment.

Since medical management never can be considered ideal unless it is carefully controlled, it can be accepted as a maxim that a trial of medical therapy for gastric ulcer should be carried out only under supervision in the hospital. Under these circumstances, environmental control is ideal and rest in bed and a carefully supervised dietary and medicinal program are possible. The dietary measures and medicinal adjuncts are those used for duodenal ulcer, with an attempt to maintain as nearly complete control of gastric acidity as possible during each 24 hours. Under such circumstances, the average benign gastric ulcer will heal in three or four weeks. An ulcer that does not demonstrate radiologic and gastroscopic evidence of healing in that period should be treated promptly by surgical means. If the ulcer has healed, as far as can be determined by roentgenography, the patient is permitted to be ambulant and is advised to follow a bland ulcer diet with intermeal milk and antacids for approximately one and one-half years. During that time, the stomach is examined roentgenographically every two to three months. If the patient remains free of symptoms at the end of 18 months and the roentgenogram of the stomach has been consistently normal, the patient can be released from close supervision. Should the ulcer recur during any phase of this period of observation, partial gastric resection is advised.

Anastomotic Ulcer

An ulcer may occur at the site of anastomosis following either posterior gastroenterostomy or partial gastric resection. In the latter instance, the lesion is rarely amenable to medical measures alone and some type of operative procedure usually is needed. In the former instance, however, the lesion may demonstrate a mild clinical course, is amenable to medical treatment, and may even heal spontaneously. Because of this, particularly if the lesion appears to be small and superficial, a trial of medical treatment often is warranted. If this course is chosen, treatment should be carried out in a hospital to allow adequate supervised care. If response to such measures is adequate and sustained, it may be possible to maintain the patient on a conservative program indefinitely. However, because of the inherent risk of further complications, undue conservatism in the handling of these lesions is to be condemned. It must be admitted that the majority of anastomotic lesions ultimately require some further surgical measure for their correction.

Complications of Ulcer

Obstruction.—Gastric retention is a common complication of peptic ulcer. This may be incident to the pylorospasm that often accompanies an active ulcer of either the stomach or duodenum or to cicatricial narrowing of the pyloric outlet. It is important to distinguish between the gastric retention due to pylorospasm, edematous pyloric obstruction, and formation of scar tissue. In the first two instances, appropriate medical measures will relieve the obstruction and subsequent adequate care permits ulcer control; in the third instance, medical measures will not suffice and an operative procedure is indicated.

Evaluation of the character of the retention and a decision as to its permanence can be accomplished best with the patient under supervision in a hospital. Putting the patient at rest in bed, allowing for frequent feedings of a nutritious noncurding diet, and aspirating the gastric contents at bedtime and in the morning before the first feeding are simple practical measures. When such treatment is given, it often will be found that a patient who at first has 500 ml. or more of retained contents at bedtime will within a few days have no significant gastric residue at this time of the day.

When such improvement occurs, it can be assumed that the obstruction is probably edematous in origin and will respond to further medical measures. The validity of this presumption can be tested several days later by means of an "eight-hour motor meal." This test is done by giving at midnight an average meal that includes some readily recognizable substance such as raisins or spinach. Eight hours later, the gastric contents are aspirated. If less than 120 ml. of secretion is recovered at that time and no food remnants are recognized in the aspirate, it can be concluded that a significant impediment to gastric emptying does not exist. However, if food remnants are evident and the amount aspirated is greater than 120 ml., it is evident that obstruction at the pylorus persists and surgical correction will be needed. Although an occasional patient with some degree of cicatricial pyloric obstruction will maintain a fairly comfortable status for some time on medical treatment, experience dictates that the wiser approach in such cases is surgical therapy.

Dehydration occurs in pyloric obstruction of long duration if considerable vomiting has been present, and there may be significant depletion of serum chloride and loss of potassium. Hemoconcentration occurs secondary to dehydration. The blood urea increases due to the lack of sufficient water for excretion of nitrogenous waste products, the increased tissue catabolism accompanying dehydration and the impairment of renal function caused by the alkalosis resulting from loss of chloride. Appropriate hydration to allow for adequate urinary output and restoration of the electrolytic balance by parenteral administration of chlorides and potassium will make surgical intervention safe.

Perforation.—Acute free perforation of a peptic ulcer is essentially a surgical problem, and this approach is favored in all cases in which the condition is recognized early. The results of this form of treatment are uniformly excellent. However, there have been patients with acute free perforation of a peptic ulcer who refused operation and yet eventually recovered. Exploring this possibility further, Bedford-Turner,[16] in 1945, treated six patients with continuous gastric suction, rest, and the parenteral use of fluids, with recovery in all. Other authors subsequently commented favorably on this method of treatment. However, in the cases in which such treatment was given, there were deaths that might have been avoided had immediate surgical therapy been employed, and unpleasant complications sometimes occurred. It is comforting to know that properly instituted medical measures can give a good chance for recovery if perforation of a peptic ulcer occurs under circumstances that preclude surgical care; however, in the average case, surgical treatment is to be preferred except in those instances when the perforation has occurred 24 hours or more previously.

Hemorrhage.—Bleeding is a common complication of peptic ulcer. In the majority of such instances, medical measures will suffice to insure recovery. This is particularly true when loss of blood is minor. In the presence of exsanguinating hemorrhage with shock and evidence of continuing brisk bleeding, a special situation confronts the physician. Although in large measure these patients will respond to medical measures, there remain those in whom the bleeding persists despite every conservative effort that may be employed. It is important to recognize this situation, because early surgical intervention will be life-saving in such patients. The decision as to the wisdom of operating during active bleeding cannot be delayed with impunity. Rarely should this decision be delayed beyond 48 hours, since the chance of recovery decreases sharply when the decision is deferred beyond that time.

The broad principles of medical therapy in this complication include rest, insurance of mental tranquility, early feeding, and

early adequate replacement of blood by transfusions of whole blood.

Early feeding in the treatment of bleeding peptic ulcer was first suggested by Lenhartz,[17] in 1904, and was later shown to have a sound basis by the observations of Meulengracht.[18] Experience has proved that the older concept of prolonged starvation in these cases has no justification.

Although some observers still advocate caution in the replacement of blood by transfusion in these bleeding patients and some even would withhold blood except in situations of dire need, modern physiologic concepts of the effect of prolonged shock in leading to irreversible changes affecting such vital functions as are inherent in the myocardium, kidneys, liver, and vasoconstrictor center call for adequate replacement of blood from the start. This approach of early and adequate transfusion not only avoids lethal complications but speeds recovery and maintains the patient in a physiologic state satisfactory for a surgical procedure at any time should persistent bleeding dictate the wisdom of such a course.

Intractability.—Many duodenal ulcers, particularly those of long duration, burrow beyond the confines of the wall of the duodenum, involving adjacent structures secondarily. Such lesions usually produce pain that is no longer controllable by reasonably adequate medical measures. Although it is possible in many of these patients to obtain fairly adequate temporary control of symptoms by strict treatment in a hospital, most of them have a return of symptoms on ambulation. Since the results of surgical treatment for duodenal ulcer in this present era are so excellent, it is not reasonable to expose a patient to the morbidity of recurrent ulcer symptoms inadequately controllable by the best available medical treatment. In any case in which an adequate medical regimen fails to provide reasonable control of symptoms and freedom from pain, surgical treatment for the ulcer is to be recommended.

Comment

Uncomplicated duodenal ulcer is properly to be considered primarily as a medical problem. With efficient application of simple well-known readily available principles of treatment and the wholehearted cooperation of the patient in their employment, satisfactory control of the lesion will be possible in a large proportion of cases.

Many drugs and measures have been suggested in the treatment of peptic ulcer. Most have added little or nothing to the time-tried principles of treatment. Unfortunately, the public is assailed by many nostrums purporting to cure peptic ulcer. It is important for the patient who has an ulcer to realize that it is unwise to speak of medical cure of his disease; instead he should strive to achieve control of it. He must understand that experience fails to support the idea that one medicine will be an easy answer to his problem and must realize that the principles of release from emotional tension and mental stress, use of a bland diet, avoidance of stimulants to gastric secretion, and efficient neutralization of acid give the best hope for control of his lesion. The patient must recognize that satisfactory treatment of his ulcer does not depend solely on his physician and the medicines prescribed but that he (the patient) also must be willing to make important concessions.

All too often the ulcer patient attempts to find release from the emotional tension that is a concomitant of his disease by overuse of alcoholic beverages, coffee, and tobacco. That alcohol and caffeine are stimulants to the production of acid is well accepted. It is only logical to exclude whatever factors tend to defeat the goal of efficient neutralization of acid. Therefore, the ulcer patient should avoid use of alcoholic and caffeine-containing beverages. Less agreement exists as to the physiologic effect of tobacco on the output of gastric juice; some investigators have reported an increase of gastric acidity,[19] whereas others have found no change or only an occasional in-

crease.[20] It appears that certain patients are hypersensitive to tobacco, and they will experience aggravation of their symptoms by the use or overuse of tobacco. Such persons should be enjoined to give up their habit. For the most part, ulcer patients are unwilling to discontinue their use of tobacco, and some compromise ordinarily must be made in regard to this factor. Moderate smoking after meals apparently is less harmful than is smoking when the stomach is empty. Clinical experience appears to bear out the truism that an ulcer patient who is willing to forego use of alcohol and caffeine-containing beverages and stop the use of tobacco completely will stand a better chance to control the symptoms than will the patient who refuses to modify his habits in this regard or who compromises in regard to them.

Although it is considered that uncomplicated duodenal ulcer is primarily a medical disease, stubborn adherence to a medical regimen in the face of a poorly controllable ulcer is to be decried. The excellent results of surgical treatment for duodenal ulcer in the hands of well-trained surgeons do not justify exposing a patient to the prolonged morbidity of an intractable duodenal ulcer.

Gastric ulcer presents a special problem because of the ever-present hazard of gastric neoplasm and the lack of a positive clinical criterion that will assure accurate recognition of the histologic character of every gastric ulcer prior to its surgical excision. Therefore, it is wise to consider this as primarily a surgical lesion. This observation is made advisedly, recognizing the fact that a majority of gastric ulcers are benign and that many of these will heal promptly in response to supervised and adequate medical treatment.

Medical measures for duodenal and gastric ulcer must include attention to rest, alleviation of tension and anxiety, dietary modification, and the control of gastric acid by reducing its formation and neutralizing it after its production. To be successful, treatment must be adequate not only during the time of activity of the ulcer but also during its periods of inactivity. Recognition of this principle necessitates lifetime cooperation on the part of the patient. Haphazard measures of treatment tolerated by the physician and haphazard cooperation by the patient doom to failure at the outset any medical regimen designed for the treatment of peptic ulcer, whatever its location.

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Evaluation of the Surgical Treatment of Intractable Duodenal Ulcer

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The hope of general agreement among physicians and surgeons in the treatment of duodenal ulcer may well be as visionary as the goal of world peace through the United Nations. Both physician and surgeon agree on the importance of the acid peptic factor in the etiology of duodenal ulcer. Both call for a spirit of cooperation in the care of problem cases. To put it bluntly, neither has much confidence in the other's treatment insofar as long-term results are concerned.

The surgeon cannot forget the changing vogues of medication. Each is hailed as the panacea for the control of ulcer. In addition, there is the implied hint on occasion that the previous "inhuman resections," made necessary by the vices of man, no longer are necessary. On the other hand, the physician's experience has convinced him that 85% to 90% or more of duodenal ulcers can be treated medically satisfactorily. He knows that time is required to ferret out the "intractable" ulcer.

Lastly, the physician has been impressed by the patients who have traded their ulcer symptoms for complaints that may be more disabling and resistant to relief than the original ulcer. His skepticism well may be enhanced by the fact that surgical reports tend to emphasize a low morbidity, mortality, and recurrence rate, with scant mention of the undesirable side-effects. Both sides agree that the control of the acid factor is paramount. However, the method of controlling the acid varies from one person to the other. With no offense intended, it might be inferred by the surgeon that a similar medical regimen is routinely applied to every patient, regardless of hydrochloric acid output. The individual surgeon, on the other hand, tends to apply his "pet" operation too routinely without individualizing the type of operation to meet the needs of a particular patient. Finally, only good results tend to be written up. Usually these observations are based on too short a period. Duodenal ulcer is so common and the disability so great that it would seem that "world" medical and surgical opinion should be more unanimous in the indication for surgery and the type of operation most likely to insure a patient freedom from digestive complaints.

The fact that the per cent of patients recommended for surgery has remained relatively constant over the years may indicate that medical therapy has not particularly increased in efficiency and that present-day physicians have been no more impressed by the results of surgery than were their immediate forebears. The failure of the surgeon to gain ground for his therapy may be due to the many variables which make a scientific comparison of the various forms of surgical treatment practically impossible. Age, race, sex, psychologic attitude, economic status, occupation, geographic location, eating habits, body weight and type, etc. are all factors which must be considered when comparing the results of any type of management. In my opinion, it is doubtful if a comparable series can be collected from the literature at the present time. These variables may well account for the obvious discrepancies in the evaluation of a particular operation which are reported by surgeons with similar experiences and reputation.

There is a wide range of opinion regarding patient satisfaction with any of the

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presently used operations. An increasing number of surgeons are no longer content with the low morbidity, low mortality, and low incidence of marginal ulceration following their operations. They are attempting more and more to evaluate the side-effects of the surgical procedure. In the past, this responsibility has been largely assumed by the medical men, who have been much more impressed by the postoperative symptoms of their patients than have their surgical colleagues.

Surgical literature continues to thrive on the good and bad points of the 75-year-old operations of the Billroth I and II types in the patient with an intractable duodenal ulcer. The late results of gastroenterostomy has thoroughly condemned this procedure, except in the occasional instance of an extremely poor-risk elderly patient with pyloric obstruction from a scarred duodenum. Over the years, as the safety of gastric surgery increased, there was a tendency to remove more and more of the stomach in an effort to further lower the incidence of marginal ulceration. While this radical approach was effecting a modest reduction in the incidence of marginal ulceration, too many patients were paying a high price for this protection in the form of digestive complaints and impaired nutrition.

The monumental experimental and clinical work carried on by Dragstedt [1] and Wangensteen [2] on the ulcer problem has been largely responsible in recent years for the diversity of the surgical attack on the ulcer problem. Changes occur slowly, since the majority of surgeons tend to utilize the operation they were taught during their training, regardless of the variables presented by the individual patient.

At the present time it is probable that the majority of surgeons in this country are satisfied with the resection of two-thirds or three-fourths of the stomach followed by gastrojejunostomy. The Hofmeister antecolic anastomosis is probably the most widely used at the moment, followed by the retrocolic Polya type of anastomosis. Walters,[3] in his support of partial gastrectomy with a Billroth II or Polya type of anastomosis, reports a high percentage of excellent or good results in a large series of cases with a 3.6% marginal ulcer recurrence rate. In contrast, he found that the use of the Billroth I procedure reduced considerably the percentage of satisfactory results and the increased incidence of recurrence several times. In both groups, results were reported on patients followed from 6 to 10 years. This length of follow-up, or even longer, is extremely important in evaluating any type of procedure.

The popularity of vagotomy combined with gastroenterostomy as a conservative, yet effective, procedure has been championed by Dragstedt. In a group of 487 patients followed for a 10-year period, the recurrence rate was 1.8% and the number of good results approximated 82%.[1] Furthermore, the operative mortality of this conservative procedure was about one-tenth that of subtotal gastric resection. Burge and Pick,[4] of the British Isles, reported a survey concerning approximately 300 patients followed seven to nine years after vagotomy and gastroenterostomy. They reported a recurrence rate of 4.25%. Only 11% of the patients lost weight following operation, compared to 47% when vagtomy and gastrectomy had been performed. While their patients were not disabled insofar as a return to hard work was concerned, they did complain of some disagreeable side-effects. Approximately 30% had an occasional short bout of diarrhea; 16% had mild dumping symptoms, and bile regurgitation was present in 13%. The authors believed their failures were due to inadequate section of the vagus nerves.

While Dragstedt, Farris, Smith, and others [1,5] continue to be very well satisfied with the procedure of vagotomy and gastroenterostomy, the initial post-World War II enthusiasm for this procedure has gradually waned. Despite this trend, the operation is attractive in that it does not decrease the gastric capacity and can be performed with

a very low mortality rate. This procedure may be the operation of choice in a poor-risk patient or when technical difficulties make resection hazardous as with an ulcer located near the common duct or in the presence of a very extensive inflammatory reaction about the pylorus. In my opinion, this conservative procedure should invariably be considered in emaciated patients, especially females, unless the patient is actively bleeding.

Perhaps the wide range of results following the use of vagotomy and gastroenterostomy can be accounted for in part by technical failures in the performance of the operation. In the first place, vagotomy must be complete. Secondly, the location of the stoma as well as its size is important to the successful outcome of this operation. The traditionally large gastroenterostomy stoma opposite the angle of the stomach may give rise to subsequent difficulty as a result of postvagotomy dilatation of the inadequately drained antrum. Inadequate drainage of the paralyzed antrum gives rise to a prolongation of the gastric phase of secretion, which may bring about a recurrent ulceration. This can be avoided and recurrent difficulties can be held to a minimum if the technical principles of the operation developed by Dragstedt are religiously followed. A small stoma approximately 1 fingerbreadth (1.5 cm.) in size and located along the greater curvature within 5 or 6 cm. of the pylorus is essential to insure good results. This may not be an easy technical procedure, since the structures about the pylorus may be adherent and difficult to mobilize.

The evaluation of failures following this procedure should include the insulin test to determine the completeness of the vagotomy. Furthermore, x-ray studies are necessary to determine the size and location of the stoma. A stoma placed too far to the left may explain the patient's recurrent difficulty, and reoperation may be indicated. Either gastric resection or closure of the existing stoma followed by the construction of a new small stoma near the pylorus may be justified along with a search for overlooked vagal fibers.

It is hoped that long-term studies in a sufficiently large series of cases, in whom the technical steps of the operation have been carried out according to the dictums of Dragstedt, will soon be available for study and comparison. The long-established antagonism to gastroenterostomy as a method of treating duodenal ulcer is not easily forgotten. The undesirable side-effects from the accompanying vagotomy has further strengthened the dislike of many surgeons for this procedure. However, the introduction of vagotomy did emphasize the factor of conservatism and swung the pendulum away from the extremely radical procedures.

It is highly probable that the decreased popularity of vagotomy and gastroenterostomy has been more than compensated for by the increased number of surgeons who combine vagotomy with gastric resection or pyloroplasty.

Weinberg[6] has found pyloroplasty of a modified Heineke-Mikulicz type, rather than gastroenterostomy, useful in promoting emptying and thus preventing gastric stasis. This procedure provides adequate drainage of the paralyzed stomach without interrupting the normal continuity of the digestive tract. He emphasized that the pyloroplasty should be done with one row of sutures in order to avoid infolding so much tissue as to compromise the patency of the outlet and thus to defeat the purpose of the operation. In more than 800 vagotomy and pyloroplasty procedures, performed in a period of nine years by Weinberg and his associates, there was a recurrence rate of 0.5%. Pylorectomy or gastrojejunostomy were performed when the duodenum was severely inflamed or markedly distorted by scar tissue.

Another group of distinguished surgeons has added vagotomy to gastric resection. Colp[7] for many years used a two-thirds to three-fourths resection of the Billroth II type. However, in 1946 he added bilateral infradiaphragmatic vagotomy after studies showing that resection of the above extent

did not always protect the patient against subsequent gastrojejunal ulceration. In a six-year follow up of 206 patients who underwent subtotal gastrectomy for duodenal ulcer the incidence of recurrence was found to be 7.7%. This percentage was practically reduced to zero in the 184 cases in which vagotomy with a Billroth II resection was employed. While complementary vagotomy performed with gastrectomy afforded added protection against recurrent ulceration, there was an increase in postoperative morbidity. He found that the percentage of dumpers was increased and that 10% of the patients developed moderate diarrhea.

Vagotomy combined with hemigastrectomy with either Billroth I or II type anastomosis has gained increasing popularity during the past five years. This trend developed from the observations of Smithwick [8] and associates, who found that gastric acidity was lowered to a minimum of vagotomy and hemigastrectomy, which included resection of the antrum. This procedure in their experience gave a decreased mortality, almost no nutritional difficulties, and freedom from recurrences in patients followed from one to six years. In a series of 135 patients having vagotomy and hemigastrectomy the mortality was 2.2%. The early clinical results were much better in this group of patients than in a series of 190 patients treated by subtotal gastrectomy alone. Smithwick prefers the Billroth II type of anastomosis with a comparatively short-loop anterior gastrojejunostomy. He believes this is the simplest and safest technique for most surgeons. On the other hand, many surgeons prefer some type of Billroth I anastomosis following vagotomy and hemigastrectomy in the belief that fewer postoperative difficulties occur if the gastrointestinal tract is restored to as near normal as possible. Edwards et al.[9] have found the operation of vagotomy and antrectomy to be highly satisfactory in the treatment of duodenal ulcer. They removed an estimated 40% of the distal stomach, followed by the Schoemaker modification of the Billroth I anastomosis. They reported the absence of recurrent ulceration in 294 patients followed 1 to 10 years after removal of 35% to 60% of the distal stomach and vagotomy.

I have been favorably impressed with the experimental evidence as well as the clinical experience reported with the use of vagotomy and hemigastrectomy.[8] This procedure controls the cephalic as well as the gastric phase of secretion, yet a capacious gastric pouch is retained. Although good results have been reported from all types of anastomosis of the gastric pouch to either the duodenum or the jejunum, we have preferred to reconstruct normal continuity by the direct end-to-end anastomosis. This provides but one suture line, avoids the occasional pitfalls associated with closure of the duodenal stump, and permits reconstruction of a normal-sized outlet.

Many surgeons are hesitant to use the Billroth I operation in any combination because the incidence of recurrent ulcer appears to be much higher than following the Billroth II operation unless 75% or more of the stomach is removed and the vagus nerves are divided. Experiences with the late Elliott C. Cutler convinced me years ago that Billroth I procedure without vagotomy would not provide sufficient protection against recurrent ulceration for the patient with an intractable duodenal ulcer. Harkins and his associates, however, have had satisfactory results utilizing the Billroth I operation without vagotomy, but they removed at least three-fourths of the stomach.[11] While this procedure became increasingly popular after World War II, as it has many times in the past; the Billroth I operation without vagotomy has again failed to become a widely accepted surgical procedure for duodenal ulcer.[10] More recently, Harkins [12] has been utilizing vagotomy and hemigastrectomy followed by a Billroth I anastomosis with the assumption that the incidence of dumping would be reduced and the larger gastric reservoir more efficient for the thin patient.

During the past four or five years I have utilized the procedure of vagotomy, hemigastrectomy, and direct end-to-end anastomosis of the gastric pouch to the duodenum. In my opinion the Billroth I type of anastomosis can be carried out with safety in the great majority of patients with duodenal ulcer. An increasing amount of stomach has been retained as the extent of the resection has been slowly decreased during these years from three-fourths to two-thirds and, finally, to 50%. As in vagotomy and gastroenterostomy, certain technical steps must not be overlooked in the performance of this procedure. The vagotomy must be complete and a repeated search made to insure completeness, lest recurrence take place. On my service three proven recurrences have already occurred following this operation and they have been proven to be associated with an overlooked posterior vagus nerve. The operations in these cases were all performed by surgeons of limited experience in the technique of vagotomy. After vagotomy the crus of the diaphragm posterior to the esophagus has been approximated as insurance against the possible development of a hiatus hernia. The technical performance of this operation as well as its safety is greatly enhanced if the stomach as well as the duodenum are extensively mobilized.

The stomach is mobilized by detaching the fundus from the diaphragm and by mobilizing the spleen after the division of the splenorenal ligament. In addition, the splenic flexure of the colon is detached and the entire omentum separated from the transverse colon. The latter step is an easy technical procedure and prevents traction on the gastric pouch following possible distention of the colon during the postoperative period. This maneuver provides direct visualization of the body and tail of the pancreas. Those surgeons experienced with the Billroth I operation are more apt to use the Kocher maneuver of freeing up the duodenum to a much greater extent than ordinarily performed. Such mobilization of the duodenum and head of the pancreas facilitates the resection of the ulcer, since the site of dissection can be mobilized up into the wound, adding to the safety of the technical procedure.

Obviously there are contraindications to any type of operation, and a resection of this type would not be indicated in an elderly poor-risk patient. Neither should it be attempted in the presence of an unusually placed ulcer, such as one located near the region of the common duct, nor in the situation of an extensive inflammatory reaction, making removal of the ulcer hazardous. These contraindications to resection are generally well understood and followed by the majority of surgeons.

There has long been considerable discussion regarding the extent of the stomach removed at the time of operation. Some surgeons have indicated they have performed radical gastric resection, yet follow-up x-ray studies have shown a third or more of the stomach to be retained. Because of these discrepancies, Coffey and Lazaro [13] and Howe and Porell [14] reported studies on landmarks that the surgeon may use at the time of operation to insure removal of approximately one-half of the stomach. The landmarks utilized were the third vein down from the esophageal junction on the lesser curvature and a point on the greater curvature where the left gastroepiploic artery comes closest to the gastric wall. Harkins has also developed a method of measurement which has been found useful in determining the amount of stomach resected.[11] More recently, Heinrich and Priestley [15] reported a method based on two measurements. The weight of the stomach removed divided by the thickness of the muscularis of the cut upper edge of the specimen provided figures which permitted them to estimate the percentage of stomach removed with an error of 5%. It is extremely doubtful that it makes any real difference as to whether 50% or 60% of the stomach is removed. It is true that a surgeon accustomed to performing very radical resections over a period of years finds it difficult to reduce the extent of resection. He has an inherent fear that

so much retained stomach may be responsible later for a recurrent ulceration.

In addition to the studies indicating the advantages of retention of half of the stomach, more emphasis has been placed upon the size of the stoma. It seems only logical that the size of the stoma should approximate that originally intended by nature in an effort to preserve or approximate the physiology of a normal digestive system. Over the years some surgeons have recommended the construction of a small stoma in the belief that this decreased the incidence of the dumping syndrome during the postoperative period. Dragstedt called attention to the desirability of constructing a gastroenterostomy stoma no larger than 1.5 cm. in diameter after vagotomy. Abbott,[16] in some very convincing studies, has shown that the construction of a stoma no larger than 2 cm. in diameter delays gastric emptying and decreases the incidence of dumping following vagotomy, hemigastrectomy, and the Billroth I type of reconstruction. A patient having severe dumping symptoms following a Billroth II type of anastomosis would be advised by many careful observers to consider the possibility of reoperation and the restoration of normal continuity by the use of a Billroth I type of anastomosis with a very small stoma. In all fairness, it should be stated that the majority of surgeons at this time tend to doubt that the size of the stoma has anything to do with the undesirable side-effects which sometimes occur following gastric resection. I am of the opinion that it is desirable for the surgeon to make a special effort to keep the stoma relatively small. I have measured the width of the duodenum and gastric pouch on a number of occasions in an effort to study this problem. Ordinarily, the duodenum is at least 4 cm. in diameter when held in a crushing clamp. The stomach is often 9 to 10 cm. in width at the point of hemigastrectomy. I have utilized the principle of von Haberer by placing a series of interrupted sutures to encirle the stomach adjacent to the point of division. This has not been a continuous reefing suture, as originally described by von Haberer (1935), but the end-result is the same. Size 0000 nonabsorbable (silk) surgical suture is used for these interrupted sutures, which are passed through the entire gastric wall in order to control bleeding and to pucker the end of the stomach until it admits only the index finger of the surgeon. This insures a lumen of approximately 2 cm. The size of the lumen no doubt is a little smaller when the two suture lines are completed. It is surprising that gastric retention has not been a problem after the reconstruction of such a small outlet, despite the fact the stomach has been paralyzed by vagotomy. This has been my experience, and the same favorable finding has been emphasized by Abbott.[16]

Perhaps any delay in gastric emptying in the early postoperative period has been deemphasized as a result of the routine use of gastrostomy after the operation. As a result of introducing the drainage tube directly through the abdominal wall and into the gastric pouch, the disagreeable side-effects of prolonged gastric suction have been done away with and accurate postoperative studies of gastric retention as well as overnight secretion are readily available.

One of the few new developments in ulcer surgery is the segmental resection introduced by Wangensteen.[2] He has reported 160 segmental resections performed during an eight-year period without a single recurrence and with a very low mortality. Of these, 87 were performed more than five years ago. In duodenal ulcers with deep craters or in a bleeding duodenal ulcer, the edges of the duodenal mucosa have been closed by a few interrupted sutures which placed the crater outside the mucosal lumen. Wangensteen has gradually decreased the extent of his segmental resection until, at the present time, he is leaving 30% to 35% of the proximal gastric pouch together with an antral pouch comprising 15% to 20% of the normal stomach. When reconstructed, the residual stomach approximates 50% of its original size. A pyloroplasty is performed to insure gastric emptying. He has adopted segmental resection as the procedure

of choice for duodenal ulcer rather than his previously recommended tubular resection. This later operation was discontinued in 1955 because of a higher than expected incidence of recurrent ulceration. This is explained by the logic that an innervated antrum gives a greater gastrin response to the ingestion of food than is observed following antral denervation. Wangensteen concludes that segmental gastric resection is a very acceptable operation because it is physiologically sound and offers many technical advantages in dealing with the difficult duodenal ulcer problem. He concurs in the opinion that prolonged follow-up studies with sound physiologic observations will be required to evaluate the most ideal surgical procedure for duodenal ulcer.

Waddell and Bartlett [17] have been studying 100 patients with duodenal ulcer who were treated by the addition of vagotomy to the procedure of antral exclusion. Early observations demonstrated side-effects similar to vagotomy and a limited resection.

It is clear that the surgeon is trying harder than ever before to evaluate the late over-all end-results of various operations in the treatment of duodenal ulcer. As this sound approach to the problem continues, it is probable that many technical variables will be introduced from time to time until the problem is solved to the satisfaction of all concerned.

As emphasized by Randall,[18] the responsibility of the surgeon to the patient extends beyond concern with recurrent ulcer rates and must include the complete rehabilitation of the patient. Admittedly, a significant number of gastric operations of any type result in postoperative complaints unrelated to the ulcer but referable to the surgical procedure. The physicians responsible in the past for the management of these late postoperative problems have been impressed by their frequency and seriousness. This may account for their conservatism in recommending surgery. However, more surgeons are seeking the ideal surgical procedure for duodenal ulcer in the hope that the patient should be able to eat anything, anytime, anywhere, and without undue limitations. Freedom from recurrent ulceration and from disagreeable side-effects which may follow certain foods, especially sweets, and the maintenance of an adequate nutrition consistent with the patient's height, weight, and physical activity are the goals of modern surgery. While the reported incidence of recurrent ulceration varies, the range is relatively narrow. This consistency is in marked contrast to the reported wide range of other disagreeable side-effects lumped together as the "dumping syndrome." While surgeons may report a similar mortality and recurrence rate for a given operation or series of procedures, they rarely agree as to the incidence of the "dumping syndrome." Special interest in these problems on the part of the surgeon combined with a searching personal interrogation of the individual patient invariably brings out a much higher incidence of postgastric surgery symptoms than is reported by the casual observer. Searching and direct inquiry often bring out a variety of symptoms and limitations which may be so mild as to be forgotten by the patient or disregarded by the observer. For years surgeons have been loathe to accept these symptoms as important unless they are relatively severe and classical, with sweating, a fast pulse, and a definite need to lie down after meals. It is doubtful that there is a wider difference of opinion in all of surgical literature than the reported incidence as well as severity of the "dumping syndrome" following any particular operation for duodenal ulcer. Unfortunately, too many surgeons in the past have been unwilling to consider these symptoms significant unless they are marked and disabling to the patient. This does not give a true index as to the incidence of this complaint following gastric surgery. Approximately 10% or less of the patients have these severe symptoms. There is evidence from careful follow-up studies that the patient has about a 50-50 chance of trading his ulcer symptoms for new symptoms, which are usually minimal and tend to lessen or disappear by the end of the first

year after surgery. Fortunately, few of these symptoms are disabling or necessarily disturbing to the patient, yet they do exist and must be accepted in evaluating the results of an operation from the patient's viewpoint. Regardless of certain limitations, 9 out of 10 patients are very happy with their results and thankful for the relief from their ulcer pain.

I am of the opinion that the patient's nutritional status late in the postoperative period may be an important index of the success or failure of any particular operation. This became apparent following a study of 203 unselected ulcer patients who were subjected to a variety of radical surgical procedures one to six years previously. This study showed that over one-half (109 of the 203 patients) failed to regain their preoperative weight. As a result of this study, the idea was developed that the patient's preoperative weight in relation to his ideal weight is essential data in planning elective gastric surgery for duodenal ulcer.[19]

The patients are grouped into one of three clinical types preoperatively. The first group consists of those who were above their ideal weight and who, in many instances, were definitely obese as a result of their intensive ulcer management. A second and much smaller group of patients consists of those persons who at one time had reached their ideal weight but as a result of their disease or some other cause were now well below their ideal weight. A third group has always been on the thin side and has never at any time in their life reached their so-called ideal weight. The ideal weight can be determined by a reference to the standard life-insurance tables. However, we ordinarily use the formula of 112 lb. as the basic weight for females and 120 lb. for males of 5 ft. in height. Four pounds are added for each inch above 5 ft. A leeway of 5 lb. above or below the calculated ideal is permissable, depending upon the body build of the person. I have found that the obese patient has the best result in respect to postoperative nutrition after surgery for duodenal ulcer. Two out of three of the Group I, or obese patients, having a 70% resection reached their ideal weight and maintained it during their postoperative period. These good eaters are able to maintain a sufficient caloric intake, and it makes little difference, in my opinion, as to what type of operation is performed. It may well be that it is beneficial to the obese patient, insofar as longevity is concerned, to have a decrease in his total body weight, bringing it closer to his ideal. One might postulate that patients who can well afford a high-caloric diet remain on the obese side and could compose a majority of the cases in a reported series, thereby insuring a high degree of success for a particular operation.

A second group of patients, whose weight has fallen perhaps as a result of pyloric obstruction to below their ideal, were disappointing insofar as their ability to regain ideal weight in the postoperative period. I formerly believed that these patients invariably gained a good deal of weight after operation, especially if obstructed. It has been my experience that only one out of three patients in this group will regain their ideal weight after a radical resection of the Billroth II type. It is apparent that the patient below ideal weight preoperatively should have a conservative resection, such as hemigastrectomy, gastroenterostomy, or pyloroplasty, with the addition of vagotomy or the segmental resection of Wangensteen.

The third group of patients are those who have always had a bird-like appetite and who are unable to maintain a satisfactory nutrition with an intact gastrointestinal tract. It is in this definite but fortunately small group that the most difficulty has arisen. Since their intact stomach was unable to insure ideal weight for the patient, it seems logical that any sacrifice of this organ by surgery would further interfere with its efficiency. Radical resection in the emaciated patients may be disastrous and should be avoided. The surgeon may be stubbornly resistant to vagotomy and gastroenterostomy, but this conservative procedure should be the operation of choice

in this particular group, except in the presence of active hemorrhage.

In summation, it may be stated the ideal weight should be given important consideration in planning the type of operation. When the patient is below his ideal weight, a conservative procedure, such as vagotomy combined with either gastroenterostomy, pyloroplasty, or hemigastrectomy, is advised. If the patient is well below his ideal weight, as in Group III, then vagotomy and gastroenterostomy should be considered unless the patient is actively bleeding. I believe the preponderance of cases in any one of these three groups may very well champion or defeat any particular operation. It is realized many patients may be on the lean side, and perhaps this is more desirable than for them to be above their ideal weight. Certainly, few patients will complain of weight loss interfering with their daily work unless they are in the older age group and are required to perform hard physical labor. However, I have been especially impressed with the number of men who will admit under direct questioning their concern if they are very much underweight. This is largely due to the fact that their friends and relatives are constantly inquiring as to their health if they appear to be thin in comparison to their preoperative nutritional status. Furthermore, it is surprising to learn under close questioning that some male patients who are on the thin side (perhaps under 135 to 140 lb.) believe that, although they feel well, they would have a little more vigor and be better able to enjoy themselves if their weight more nearly approximated their ideal. Furthermore, the older age group is afraid their economic security might be jeopardized if any suspicion of ill health is held by their employers. I believe that the eating habits and nutritional status of the patient in relationship to this ideal weight are extremely important considerations preoperatively, as they are postoperatively. The physician, surgeon, dietician, and family must be concerned with the patient's dietary adjustment and weight trends after operation, lest the patient develop a dietary pattern which produces symptomatology and, more rarely, an unhappy dietary cripple. The symptoms of dumping may be overemphasized during the early postoperative period, as a result of everyone's enthusiasm to prepare the patient for the postoperative adjustment period. It is desirable to point out to the patient that the traditional American breakfast should be reversed, i. e., fat and protein, which are supplied by buttered toast and fried eggs, should be taken preceding orange juice or sweetened cereals.

I believe every patient having a gastric operation should be followed very closely, and, in order to accomplish this, a rather detailed form has been developed which the patient completes and returns at the end of six weeks, three months, six months, one year, etc. This form includes detailed information regarding his eating habits, response and limitations to various foods, and any peculiar symptoms. This type of follow-up is reasonably satisfactory, but a personal interview by a number of persons is required to evaluate a particular operation thoroughly. Such observations over the years have convinced us of the superiority of the conservative procedures over the very radical resections.

Recently I have been interested in studying a series of patients in this clinic who have had the conservative type of procedure combined with a small stoma. Every patient had been operated on at least one year previously. In addition to our own interrogation, the patients were questioned separately by a dietitian and a psychiatrist interested in hypnotism. In general, my group has been pleased with the results of the operation. Likewise, the great majority of these patients expressed the wish that their physician had suggested surgery many years earlier, since they were grateful for the relief from the pain of their ulcer.

Although the early results of vagotomy, hemigastrectomy, small stoma, and gastroduodenostomy are good, it must be admitted that this is not a perfect operation.

While vagotomy does permit a more conservative gastric procedure, it produces some undesirable side-effects, which include a tendency toward diarrhea and an increase in the incidence of dumping. My current studies show that slightly more than 50% of the patients are symptom-free. While approximately 90% were very pleased with the results of their operation, it was found that over 40% had some limitations or symptoms from their diet. This high percentage includes patients who have any type of digestive complaint, regardless of how minor, which developed after gastric surgery. The commonest complaint appears to be sensitivity to dairy produce and sweets. When the patient who is below his ideal weight or who continues to lose weight after gastric surgery is being questioned, usually it can be brought out that these patients have a limited capacity or a food sensitivity which many times has resulted in a marked decrease in their caloric intake.

The weight trends were particularly gratifying in those patients having vagotomy hemigastrectomy and a small-stoma gastroduodenostomy. While the majority of the patients who weighed more than 145 lb. prior to operation lost some weight, the majority below this figure gained. There was a definite increase in the percentage of patients who either held their ideal weight or who reached their ideal weight in comparison to patients who had a more radical resection combined with the Billroth II type of anastomosis.

These satisfactory weight trends were rather surprising in view of the fact that almost 8 out of 10 of the patients drank coffee and smoked after operation. Excessive smoking and intake of caffeine-containing beverages appear to be accepted by most patients and physicians alike. Furthermore, about the same percentage of patients enjoyed alcoholic beverages in one form or another. While the occasional "problem cases" would most certainly be improved by discontinuing smoking and the avoidance of liquids with their meals, the majority were not particularly disturbed, judging from their absence of symptoms and from their nutritional status. The ideal gastric operation should allow the patient to enjoy some of these minor vices to a modest degree.

Surgeons are becoming increasingly critical in their evaluation of the late results of the surgical treatment of duodenal ulcer. The safety of modern surgery combined with a low incidence of recurrent ulceration suggests a wider acceptance of surgery in the management of the "intractable" duodenal ulcer. The trend toward conservative resections should further decrease the incidence and severity of the so-called postgastrectomy syndrome. The importance of avoiding a radical gastric resection in a thin person cannot be overemphasized. The role of vagotomy and the small stoma in providing a happier patient free of ulcer symptoms, dietary inhibitions, and disagreeable postsurgical side-reactions are under intensive evaluation. While the perfect operation for duodenal ulcer has not been developed, the great majority of patients are grateful for their liberation from ulcer pain, so grateful, in fact, that wider acceptance of earlier surgical therapy is suggested in the management of the "stubborn case" of duodenal ulcer.

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The Use of Serum Protein Electrophoresis in Clinical Medicine

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Human plasma is a complex solution containing many proteins, probably hundreds, some of which are present only in trace quantities. The distribution of these proteins in the normal adult shows an amazing degree of uniformity. However, in disease states considerable variation in the quantity of the individual plasma protein components takes place, which is referred to as *dysproteinemia*. Less frequently, certain qualitatively abnormal proteins may develop as a response to disease, and these proteins are referred to as *paraproteins*.

These variations in plasma proteins in disease have intrigued clinicians since the early salt fractionation of human serum at the turn of the century. In 1921, Howe,[1] utilizing 21.5% sodium sulfate as a simple method of fractionation, precipitated a protein from serum which was defined as "albumin." This quantity of "albumin" subtracted from the total serum proteins (corrected for nonprotein nitrogen) represented "globulin." These two fractions related to the total serum protein have been referred to as the "AG ratio," and with minor variations this method to this day has been used clinically as a method of evaluating dysproteinemias and paraproteinemias in disease states. This despite the fact that with refined methods of fractionation it has long been recognized that Howe's "albumin" fraction was entirely inhomogeneous, containing not only albumin but large quantities of globulins.

Until 1937 no practical refinement of methodology was suggested to improve on the obviously limited information obtained from the "AG ratio." In this year Tiselius[2] presented his method for the electrophoretic separation of serum proteins. This method depended upon the fact that different serum proteins possess characteristically different net surface electrical charges. These serum proteins, placed in an electrical conductive solution, through which a source of direct current is passed, migrate at a rate determined by this net surface electrical charge. The migration of the proteins is recorded by a complex system of optics. By this method serum proteins were separated into five major fractions, according to their rate of migration in the electrical field, as albumin, α_1-globulin, α_2-globulin, β-globulin, and γ-globulin. A sixth fraction was described and called ϕ-component, which migrated at a rate between β- and γ-globulin and was composed primarily of fibrinogen and therefore was considerably reduced when serum instead of plasma was analyzed. There were many limitations to the clinical applicability of this method because of its complexity, the considerable cost of the apparatus, the need for well-trained personnel, and the time consumed in a single analysis. One other limitation was that serum or plasma showing lipemia or increased turbidity could not be analyzed, owing to interference with the optical system of the apparatus. Therefore, despite the fact that the limitations of the "AG ratio"

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had been amply demonstrated, this technique lacked the facility of use necessary for clinical application, except at an investigative level.

This dilemma was solved in 1950 by Cremer and Tiselius,[4] Turba and Enenkel,[3] and Durrum,[5] who applied the principle of electrophoresis to a solid medium, in this case filter paper. Their work had been stimulated by previous studies applying this method to the separation of dyes,[7] snake venom,[8] amino acids,[3,36] and peptides.[6]

The free, or boundary, electrophoresis method of Tiselius was therefore replaced by similar migration of proteins on the supporting media of filter paper. This technique is referred to as *zone electrophoresis*. By this simple inexpensive method serum or plasma is applied to filter paper wet with an electrolyte solution capable of carrying a direct current. The proteins in solution (serum, plasma) applied to this filter paper then migrate in a manner similar to boundary electrophoresis. Again the mobilities of the protein fractions are determined by their net surface electrical charge. At the completion of a period of migration, the filter paper is removed from the apparatus, dried in a hot-air oven to fix the proteins, and stained with a variety of dyes, depending upon the type of serum proteins to be determined, be it unlinked protein, lipoprotein, or mucoprotein. In the routine staining procedure with bromphenol blue, the five major components (albumin, α_1-, α_2-, β-, and γ-globulins) are identified in normal human serum. The density of the staining reaction bears a direct relation to the quantity of the protein fraction and therefore represents a method of quantitation of these serum protein fractions. This quantitation is refined over and above mere visual observation by passing the stained filter paper beneath a photoelectric cell and plotting the density of the staining reaction for each fraction. The pattern that is developed by this photoelectric scanning bears a very close similarity to the original boundary electrophoresis pattern of Tiselius. The major difference is that lipoproteins and mucoproteins are not included in the routine protein staining method and may be stained for separately with appropriate stains, whereas in the boundary method of Tiselius these lipoproteins and mucoproteins are included with other serum proteins in a summation effect. The theory and methodology of filter-paper electrophoresis are extensively and completely reviewed by Kunkel and Tiselius [15]; Block, Durrum, and Zweig,[49] and others.[13,14,16-19,21,24,25,28] *

Obvious advantages of filter-paper electrophoresis are the initial low cost of the apparatus, the small volume of serum necessary for analysis, the speed of analysis, the ease of running multiple samples simultaneously, the use of relatively unskilled technical help, the reproducibility of the method, the ease of simultaneous comparison of samples, and the facility of differentiating types of proteins, such as lipoproteins and mucoproteins. Knowing the principles of filter paper electrophoresis, one might well design and build his own apparatus; however, excellent commercial apparatuses are available at reasonable cost.

It is beyond the scope of this paper to include all of the hundreds of published contributions of the experimental and clinical applications of this method. I have included the experience of my laboratory with this method over the past six years, with observations made by others where they seem pertinent. The clinical material was either observed at the bedside by me or physicians with whom I am closely associated (Drs. Charles A. Doan and Bruce K. Wiseman) or, where this was not feasible, a complete review of the hospital and autopsy records supported the acceptance of the clinical diagnoses. In all, approximately 7000 serum samples have been examined in this laboratory and have been interpreted by me. Many of these samples represent serial studies on individual patients. All samples have been run in duplicate with standard bromphenol blue

* The methods used in this report are recorded in the Appendix.

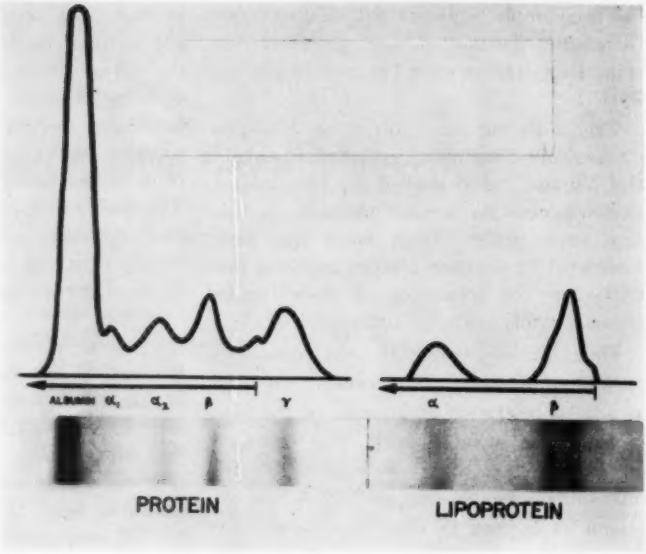


Fig. 1.—A typical normal serum electrophoretic pattern on filter paper stained with bromphenol blue for protein and Sudan Black B for lipoprotein. Photoelectric scanning patterns appear above the corresponding stained pattern. The arrow indicates the direction of migration, and the small perpendicular line at the tail of the arrow indicates the point at which the serum was originally applied to the filter paper.

staining as well as lipoprotein staining of the duplicate with Sudan black B.

Normal Serum Electrophoretic Patterns [20,26,27,29,37-54]

With the methods described in this paper there are minor variations in the electrophoretic pattern of serum proteins in apparently healthy persons. Figure 1 shows a typical normal protein and lipoprotein pattern taken from a healthy adult with the photoelectric scanning of these patterns. The normal serum protein pattern is composed of five main components (Fig. 1). Albumin, with the fastest electrophoretic mobility, is also the major component, representing approximately 66% (60%-70%) of the serum protein. It is homogeneous as characterized by the narrowness of the band on filter paper and subsequently of its scanning pattern. Such homogeneity is characteristic of greatly purified proteins and therefore suggests, when present, a single protein fraction. Conversely, a broad or heterogeneous band suggests more than one protein component, but with each component having a rather similar electrophoretic mobility. Alpha$_1$-globulin, which is in close proximity to albumin, is the second component and accounts for 3% (2%-5%) of the serum proteins. Alpha$_2$-globulin, the next component in relative mobility, represents 7% (5%-10%) of the total pattern, and for the quantity present it is rather wide, indicating some degree of heterogeneity. The fourth component in relative mobility, β-globulin, represents approximately 9% (8%-12%) of the serum protein and is characteristically a narrow band, while the last or slowest component, γ-globulin, represents 12% (10%-15%) of the total protein and is usually very wide, suggesting a great degree of heterogeneity. It must be remembered that electrophoretic analysis of serum proteins is a method of characterizing different serum proteins based on *one* physical-chemical characteristic, namely, the net surface electrical charge of the protein. It is therefore understandable that very dissimilar proteins may have the same net surface electrical charge and therefore migrate in an electrophoretic analysis as identical proteins. The terminology of albumin and the different globulins is therefore somewhat arbitrary but surely superior to the "AG ratio." The commonest variation seen in the electrophoretic pattern of apparently healthy persons is in the

γ-globulin fraction, which may show increases in quantity to over 20% of the total protein in apparently healthy persons.[33] Other minor variations are commonly seen in the α_1- and α_2-globulin fractions without apparent clinical significance. Hemolysis present in serum samples produces an abnormally high β-globulin as an artifact produced by migration of plasma hemoglobin.[22] Bilirubin, when present in the serum of jaundiced patients, will be seen on the unstained strip in the area of albumin and α_1-globulin.

When a duplicate paper strip is stained for lipoprotein with a dye having an avidity for the lipid component of the lipoprotein, two major fractions are seen: one, with a mobility at the trailing edge of albumin and occupying a portion of the α_1-globulin position, which is called α-lipoprotein, and a second, at the β-area, called β-lipoprotein. A third fraction, which is nonmigrating and therefore appears at the point of application, probably represents chylomicrons and is referred to as the 0-fraction.[65] These first two fractions are shown in Figure 2 superimposed on a normal protein electrophoresis pattern to show the mobility relationships. By extremely careful photoelectric scanning a fourth component may be observed midway between α- and β-lipoprotein, representing 2%-3% of the total lipid-staining material. In certain disease states a lipoprotein in large quantity occurs in this area either as an increase of this 2%-3% fraction or resulting from shift of β-lipoprotein to the α_2-position. This has not been seen in normal persons. Kunkel and Slater [66] and others [67-78] have reported detailed studies on the zone electrophoretic analysis of lipoproteins in normal humans.

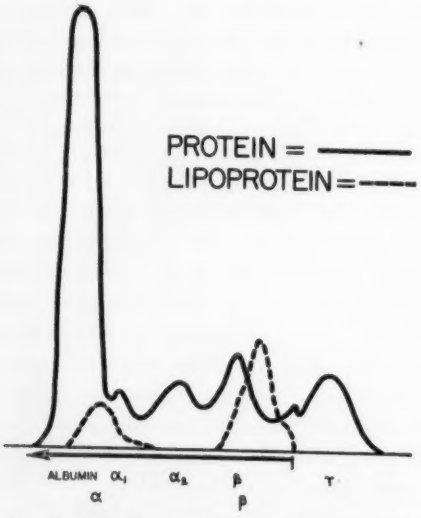


Fig. 2.—Typical scanning of electrophoretic pattern of normal serum. The lipoprotein pattern is superimposed on the protein pattern to show their relative electrophoretic mobilities.

Glycoproteins or polysaccharide-linked proteins have been stained for on filter-paper electrophoresis by Köiw and Grönwall,[79] with use of the method Hotchkiss [80] had previously applied to fixed tissues. In our laboratory this method has been difficult to reproduce and quantitate and, because of labile reagents, impractical for routine clinical use. Oxidation in room air quickly fades the staining intensity and background staining of nonprotein containing filter paper further complicates interpretation. Neuhaus [81] and Novi [82,83] have reported on its use. Also the method has found application with identification of myeloma proteins (see following material).

As a control on the actual techniques of paper-strip electrophoresis a pool of normal serums should be available, and such a pooled normal control should be run on each paper-strip electrophoretic apparatus whenever an unknown serum is to be analyzed. Despite the efficiency of the photoelectric scanning method, such a control will serve as not only a comparison but as a ready reference for the stability of other variables in the technique, such as buffer solution, drying methods, and staining methods. Any attempt at quantitation of serum electrophoretic analysis from disease states should be made only in reference to such a normal control. On all subsequent figures in this paper, abnormal serum electrophoretic patterns will be shown superimposed on a diagramatic representation of a normal serum control pattern.

The present report deals primarily with an adult population of patients. Serum proteins show variations related to age, especially at early ages. The serum proteins of the fetus have been examined electrophoretically by Bergstrand and Czar [35] and shown to be similar to the newborn infant except for a component migrating between albumin and α_1-globulin representing 10% of the total serum protein. This disappears shortly after birth and is not seen in the serum of children or adults.

The serum of the *newborn infant* shows in comparison to the adult a decreased albumin; a sustained elevation of α_1-globulin during the first six years of life; α_2-globulin and β-globulin increased in the infant and returning to normal in childhood; γ-globulin increased at birth and dropping significantly at 1 to 2 months of age, returning to normal adult levels only at the end of childhood, and, finally, β_1-lipoprotein elevated at birth above adult levels.[23,27,32,34] These physiologic variations are of significance in evaluation of dysproteinemias of infancy and childhood.

The serum protein changes attributed to *pregnancy* have been analyzed electrophoretically by Lagercrantz,[55] Corzell,[56] and others.[52,57-64] In general, as pregnancy progresses, albumin and γ-globulin decrease, while α_1-, α_2-, and β-globulin increase until delivery. In a small number of observations in our laboratory α_2-globulin and β_1-lipoprotein increase would appear to be a significant change. Three pregnant patients with chronic Hodgkin's disease whose serum electrophoretic analyses were repeatedly studied showed a minimal α_2-globulin elevation even when Hodgkin's activity was present, which is known to be associated with marked increase of α_2-globulin.

The "AG Ratio" [30]

As previously mentioned, the conventional "AG ratio" of serum proteins depends upon an estimate of "albumin" obtained by salting out. This "albumin fraction" subtracted from the total protein represents the "globulin" fraction of the AG ratio. While it has been shown previously that the "albumin fraction" of Howe contains certain globulins in significant proportions, I examined 114 unselected individual serum samples sent to the University Hospital clinical laboratories for the determination of total protein and AG ratio. Taking the whole serum and the "albumin fraction" so determined by this salting-out method, I performed simultaneous electrophoretic comparisons. Figure 3 shows a representative serum electrophoretic analysis of the whole serum and "albumin fraction" of one such patient. It is to be noted in this superimposed scanning that not only has the albumin been salted out but also significant quantities of α_1-, α_2-, and β-globulins. Such discrepancies are magnified in cases of renal disease, where the simultaneous occurrence of reduction in serum albumin and increase in α- and β-globulins are very significant, and therefore falsely high determinations of serum albumin are reported by the Howe method. Such examples give added impetus to the use of paper-strip electrophoretic analysis of serum proteins.

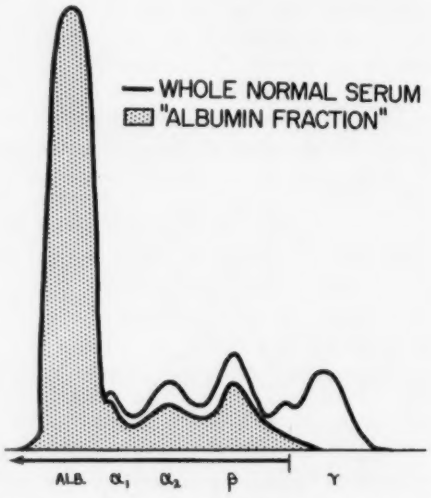


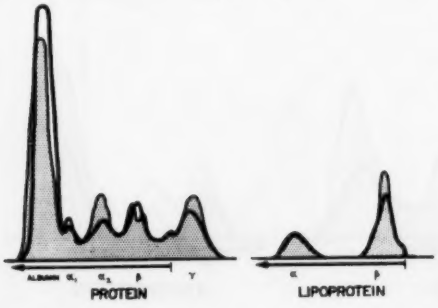
Fig. 3.—Electrophoretic pattern of whole serum and "albumin fraction" (see text).

Abnormal Serum Electrophoretic Patterns

Serum albumin and most of the globulins with the exception of γ-globulin are, according to Miller,[9-12] manufactured in the liver, and γ-globulin is manufactured by certain cells of the reticuloendothelial system. Serum proteins are lost from the body either through large denuded skin areas, such as in severe burns, or by proteinuria resulting from renal disease. While these statements are somewhat general, it follows that one would then suspect dysproteinemias to occur in diseases affecting the manufacturing sites (liver and reticuloendothelial system) and diseases causing protein loss (renal disease) and that the diagnostic application of serum protein electrophoresis would be most rewarding in diseases of these organ systems.

In practically all other organic disease entities, minor or major dysproteinemia is observed. These changes are diagnostically nonspecific but (1) confirm the presence of organic disease and (2) aid objectively in the evaluation of the course of disease. These nonspecific changes are decrease in the quantity of albumin and, rarely, increase in this component[31]; increase in α_1- and α_2-globulin; decrease of β-globulin and actual "splitting" of β-globulin into β_1- and β_2-globulin, and, lastly, heterogeneous or wide-band increase of γ-globulin. These changes of nonspecific nature make up a pattern referred to in this paper as a "stress pattern" (Fig. 4).

Fig. 4.—Normal serum electrophoretic pattern with nonspecific or "stress" pattern in shaded area: (1) 10%-15% decrease in albumin; (2) 10%-100% increase in α_1; (3) 10%-100% increase in α_2; (4) "splitting" of β; (5) increase in γ; (6) increase in β-lipoprotein. (In this and all subsequent patterns the patient's pattern will appear as a shaded area superimposed on a diagrammatic representation of a normal serum pattern.)



Diseases of the Hepatobiliary System[84-118]

Characteristic serum electrophoretic patterns are seen in certain liver diseases related to abnormal protein synthesis and are extremely helpful in the differential diagnosis of jaundice. In *cholelithiasis* uncomplicated by cholecystitis (five cases) a normal pattern is observed. In acute *cholecystitis*, much as with any infectious disease, minor nonspecific changes may be observed (three cases), characterized initially by elevation of α_2-globulin and later by elevation of γ-globulin. Only if common duct or intrahepatic obstruction is present to complicate the clinical picture is there change β-lipoprotein. Increase in the quantity of in lipoproteins shown as an elevation of serum bilirubin will be apparent on the unstained paper strip migrating in the albumin and α_1-globulin area. One case of carcinoma of the head of the pancreas, originally diagnosed prior to electrophoretic analysis as viral hepatitis in a young man, showed only marked elevation of β-lipoprotein on serum electrophoresis and very minor changes of other liver function tests despite intense jaundice and was therefore subjected to surgery to confirm his diagnosis (Fig. 5).

Viral hepatitis,[85,88,97,112,115,118] whether of serum or infectious variety, shows a pattern of progression as seen in all infectious diseases. Three cases of infectious hepatitis followed for four months in one family as well as seven cases followed for a shorter period show the need for serial observations of the serum electrophoretic pattern much as with any other test of liver function. One of these patients observed in the prodromal phase prior to the onset of clinical jaundice showed a significant increase in the α_2-globulin. In cases followed by serial observations decrease of albumin 20%-30% from control serums occurred with the onset of jaundice, together with elevation of α_2-

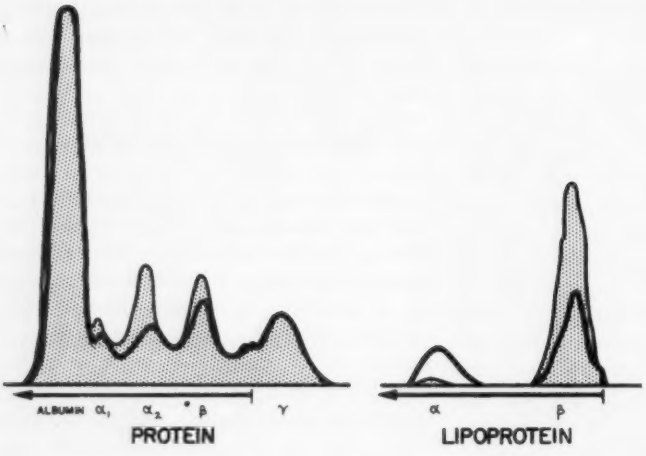


Fig. 5.—Electrophoretic pattern of serum from 26-year-old man with carcinoma of head of pancreas with obstructive jaundice. Note nonspecific changes of α_1-, α_2-, and β-globulins and significant increase in β-lipoprotein.

globulin, minor variations in β-globulin, and no apparent change of γ-globulin. As the disease progresses, the previously mentioned findings become more pronounced, especially with considerable decrease in albumin and with a gradual rise in γ-globulin. The elevation of γ-globulin, which is of wide band or heterogeneous character, persists for weeks to months after clinical improvement and with the return of liver function tests to normal. With the onset of the rise of γ-globulin, there may be a transient decrease in β-lipoprotein (Fig. 6). If isolated electrophoretic analyses are made, they must be interpreted in view of the clinical stage of the disease.

The characteristic pattern of advanced hepatic parenchymal disease, regardless of etiology, shows a marked decrease of albumin, decreased or increased α_1-globulin, decreased α_2- and β-globulins and increase of γ-globulin. Alpha-lipoprotein may be normal and β-lipoprotein markedly reduced or absent. This is to be expected, when this organ which manufactures albumin and α- and β-globulins, is grossly damaged. The increase in γ-globulin seen in hepatoparenchymal disease is not understood.

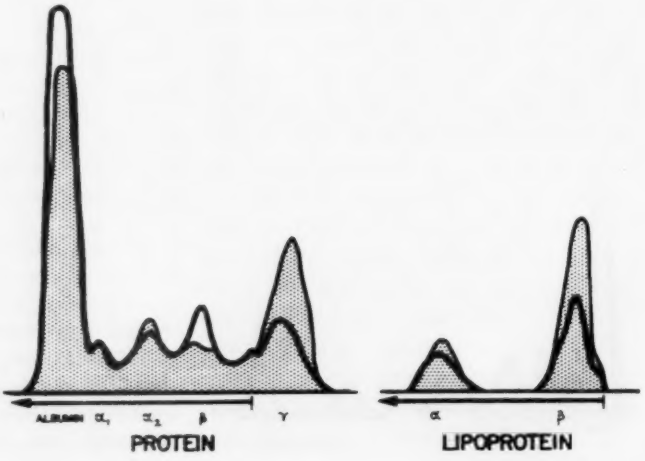


Fig. 6.—Electrophoretic pattern of serum from one member of a family of three with infectious hepatitis during the second week of the disease. Note decrease in albumin and increase in γ-globulin and β-lipoprotein.

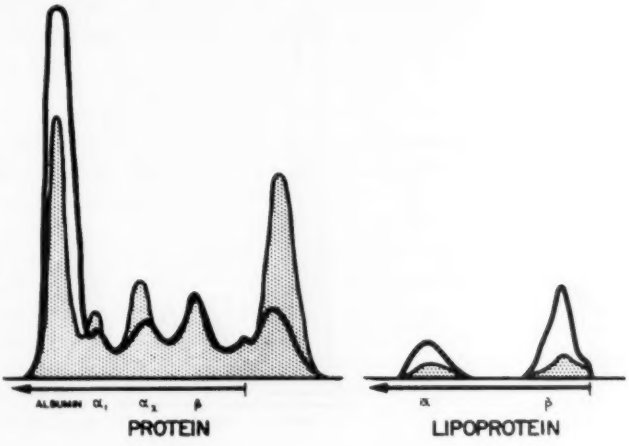


Fig. 7. — Electrophoretic pattern in 11-year-old child with postnecrotic cirrhosis proven at laparotomy. Note decrease in albumin, increase in α_1- and α_2-globulin, marked increase in γ-globulin, and decreased α- and β-lipoproteins.

In 10 cases of *postnecrotic cirrhosis* proven by biopsy or necropsy, the electrophoretic pattern of severe parenchymal hepatic disease is seen with superimposed nonspecific changes characteristic of infectious diseases. Figure 7 shows the electrophoretic pattern of an 11-year-old girl proven to have postnecrotic cirrhosis at the time of splenectomy for a secondary hemolytic anemia. On prolonged rigid bed rest and dietary management, her pattern gradually returned to normal along with continued improvement of her clinical picture and tests of liver function. Significance decreases of albumin are seen varying with the intensity of the disease; α_1- and α_2- and β-globulins are usually elevated, suggesting the nonspecific superimposed changes of infectious diseases in general, and γ-globulin may be elevated as much as five to seven times normal levels and be quite heterogeneous. The β-lipoprotein characteristically is decreased and in some severe cases may be virtually inapparent except to careful photoelectric scanning.

Fifty-three cases of Laennec's or *nutritional cirrhosis* [84,86,90-96,98-111,113,115-117] show a marked decrease of albumin, variable increases and decreases of α_1-globulin (not necessarily correlated with the quantity of

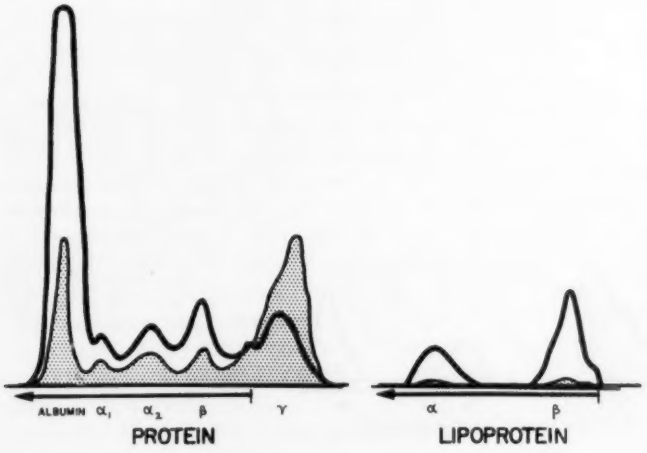


Fig. 8.—Electrophoretic pattern of serum from patient with Laennec's or nutritional cirrhosis proven by surgical biopsy. Note marked decrease in albumin and α_1-, α_2-, and β-globulins; marked heterogeneous increase in γ-globulin, and marked decrease in α- and β-lipoproteins.

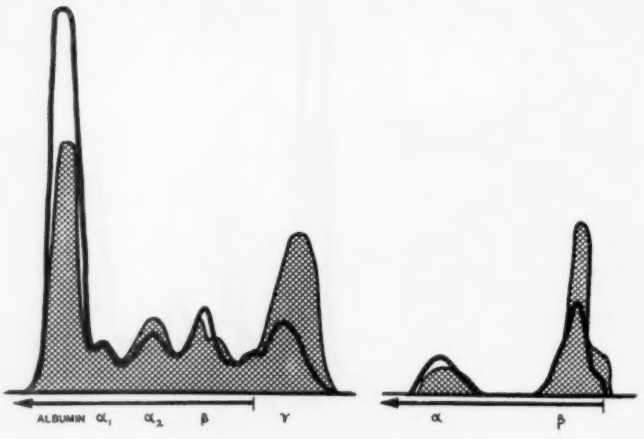


Fig. 9.—Electrophoretic pattern in lupoid hepatitis. Note decrease in albumin, increase in α_2-globulin splitting of β-globulin, and increase of γ-globulin and β-lipoprotein.

albumin present) and α_2- and β-globulin, and marked elevation of γ-globulin of a heterogeneous type as much as five to seven times the range of normal serum in advanced stages of the disease; α-lipoproteins may be reduced, and β-lipoproteins are markedly reduced and may not be apparent to visual observation of the paper strip (Fig. 8). If some degree of intrahepatic obstruction is present, then the β-lipoprotein may be significantly elevated above normal values. Again it must be mentioned that as with any other test of liver function the changes of the electrophoretic pattern are correlated with the severity of the disease and serial observations are more informative than isolated analyses, especially in a disease of such chronicity as nutritional cirrhosis.

One case of *lupoid hepatitis* followed for over a year, with hepatitis and with positive L. E.-cell preparations, showed an electrophoretic pattern similar to far-advanced cirrhosis while her clinical appearance was that of an active well-nourished woman (Fig. 9). Her β-lipoprotein increase was paralleled by an elevated serum cholesterol.

In our three cases of *biliary cirrhosis* the pattern of parenchymal hepatic disease is seen, with the exception that β-globulin

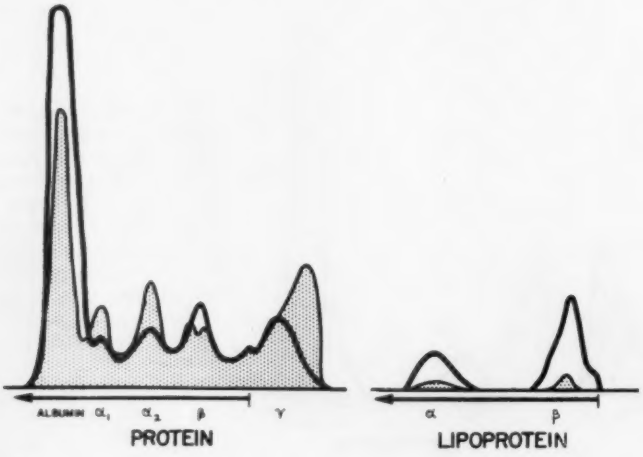


Fig. 10. — Electrophoretic pattern of serum from patient with carcinoma of liver proven by surgical biopsy. Note decreased albumin and β-lipoprotein and increased γ-globulin but increased α_1- α_2- globulins and "split" β-globulins.

may be slightly elevated and, significantly, β-lipoprotein will be markedly elevated without a demonstrable "α_2-shift." Definitive studies have been reported by Sterling and Ricketts [87,105] and Kunkel and Ahrens [89] on a wider experience with this disease.

Primary or *metastatic tumors* of the liver show only a nonspecific decrease of albumin and increase of α_2- and γ-globulins if they involve small areas of the liver. However, when the liver is largely replaced by tumor, the pattern of hepatic parenchymal disease is noted with reduced albumin, increase of γ-globulin, and decrease of β-lipoprotein (Fig. 10).

Three cases of *hemochromatosis* of moderate clinical severity proven by biopsy and serum iron studies showed a pattern similar to patterns seen in portal cirrhosis.[114]

Therefore, in the differential diagnosis of jaundice as well as the evaluation of the clinical course of hepatic disease serum protein and lipoprotein electrophoresis may be a most valuable adjunct to present tests of liver function.

Diseases of the Reticuloendothelial System

The serums of over 600 patients with disease of the reticuloendothelial system have been examined by electrophoresis. It will be recalled that this system is concerned, as is the liver, in serum protein synthesis. Therefore, disease affecting the reticuloendothelial system would be expected to produce changes in the serum electrophoretic pattern. Aside from the nonspecific changes seen in many diseases, the γ-globulin fraction is most seriously changed in reticuloendothelial system diseases. In fact, significant decreases in the quantity of γ-globulin, in the absence of nephrotic syndrome, practically speaking signifies disease of the reticuloendothelial system.[175] The incidence of hypogammaglobulinemia in diseases of the reticuloendothelial system is 22%, whereas all other diseased patients show an incidence of less than 1% if nephrotic syndrome is excluded. This incidence of hypogammaglobulinemia is even more striking in certain reticuloendothelial system diseases, namely, chronic and acute lymphatic leukemia, lymphosarcoma, and multiple myeloma. In chronic lymphatic leukemia the incidence approaches 50%.[134, 169,170,175] This finding is not unexpected, as most investigators believe that γ-globulin as well as some portions of β-globulin are synthesized by elements of the reticuloendothelial system (plasma cells, lymphocytes, and phagocytic clasmatocytes). Overwhelming disease of this system apparently interferes with synthesis of these proteins. A significant degree of hypogammaglobulinemia is said to exist, in the present communication, if this fraction is decreased 30% or more below the level of a pooled normal control serum analyzed, stained, and scanned by photoelectric methods simultaneously with the patient's serum.

In *acute leukemia* (110 cases) nonspecific albumin, α_2- and β-globulin changes in the electrophoretic pattern are frequently seen and roughly parallel the severity of the disease. Interpretation is complicated by the high incidence of bacterial infection in these patients which nonspecifically modified the pattern. Hypogammaglobulinemia, seen in all forms of acute leukemia, is found to be slightly higher in incidence and in the degree of deficiency in *acute lymphatic leukemia* (Fig. 11). Acute lymphatic leukemia in remission will show a normal serum protein pattern. *Acute monocytic* and *acute myelogenous leukemia* frequently, besides their nonspecific changes, show strikingly increased γ-globulin of a diffuse or heterogeneous type.

Chronic lymphatic leukemia (123 cases) shows the highest incidence of hypogammaglobulinemia (Fig. 12). A careful serial observation study of 113 of these patients shows that the degree of hypogammaglobulinemia is not correlated with the degree of bone marrow infiltration by lymphocytes, total leukocyte count of peripheral blood, known duration of disease, or the method of treatment. It is also not well correlated

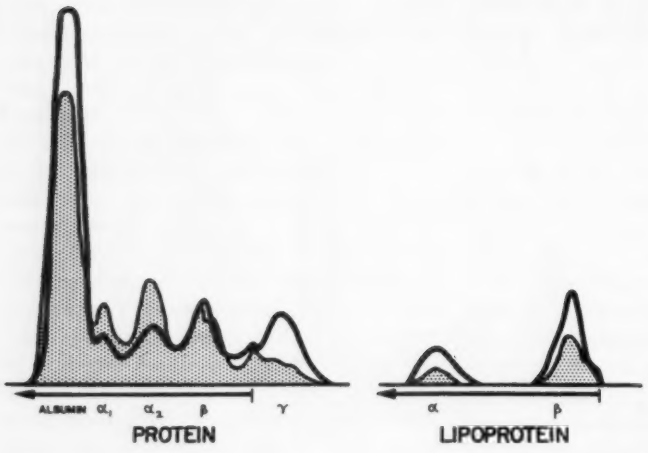


Fig. 11. — Electrophoretic pattern of serum from patient with leukolymphosarcoma (acute lymphatic leukemia) with secondary infection. Note the significantly decreased quantity of γ-globulin as well as other nonspecific changes.

with a significant increase in the rate of incidental infections in this group of patients. *Chronic myelogenous leukemia* (54 cases) shows only nonspecific changes in the serum proteins with an increased incidence of hypogammaglobulinemia, as seen in many other diseases of the reticuloendothelial system.

Polycythemia rubra vera (23 cases) shows no characteristic electrophoretic changes.

Patients with *lymphosarcoma* (55 cases) show a high incidence of hypogammaglobulinemia. There is evidence to suggest that this finding may be present as long as four years before diagnosis of this disease.[175] Other nonspecific changes may be present as the disease progresses in severity (Fig. 13). It has been particularly helpful in my hands in the diagnosis of two cases of gastrointestinal sarcoma. One case with hypogammaglobulinemia of four years' duration undoubtedly had a small intestinal sarcoma which was not diagnosed until obstruction of the bowel occurred despite six negative small-bowel x-ray examinations. Another case thought to have chronic gastritis, whose serum showed hypogammaglobulinemia, was operated on and found on microscopy to have an infiltrative lym-

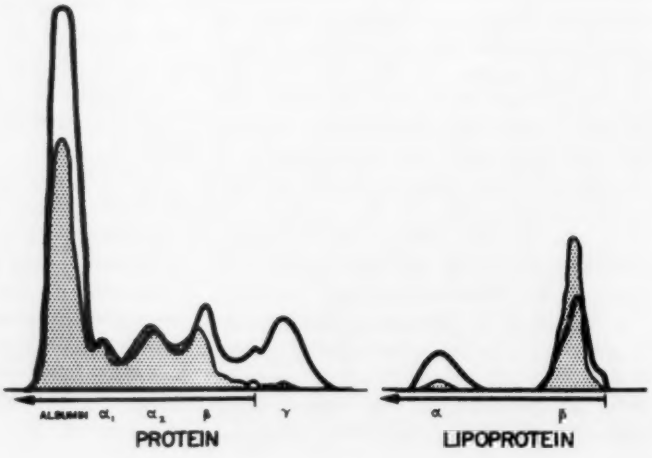


Fig. 12.—Chronic lymphatic leukemia. Cohnheim type. Note significant decrease in albumin and β-globulin and near absence of γ-globulin.

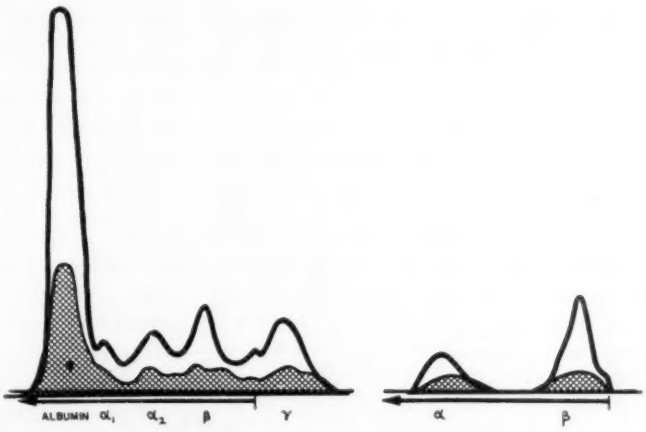


Fig. 13. — Lymphosarcoma, terminal case, showing marked decrease of all protein components, as seen in many terminal malignancies.

phosarcoma of the stomach. Therefore, patients with hypogammaglobulinemia now suggest to the clinician the possibility of some reticuloendothelial system disease and among reticuloendothelial system diseases acute or chronic lymphatic leukemia and lymphosarcoma and conversely would suggest in suspect lymphoma that Hodgkin's disease would be unlikely.

In three cases of visceral involvement of liver and spleen and generalized lymphosarcoma with ascites and pleural effusions a curious homogeneous γ-globulin has been observed repeatedly. This homogeneous protein resembles M-protein of myeloma but is usually present in quantities much smaller than seen in myeloma of similar severity and also has a very limited avidity for lipid staining as compared to the marked avidity of M-protein for the lipid stain.

A recent report [156] and a symposium on this problem [214] have called attention to a group of patients with lymphosarcoma who show such homogeneous proteins simulating M-protein. In my experience the occurrence of the truly homogeneous abnormal proteins simulating M-protein is rare, whereas significant heterogeneous increase of γ-globulin is not at all uncommon in this disease as in many others. One curious case of generalized lymphosarcoma who periodically shows circulating plasma cells in his peripheral blood had a total serum protein of 12.0 gm. but showed only a heterogeneous increase in γ-globulin as seen in other lymphosarcomas or even hepatic cirrhosis. Therefore, careful electrophoretic analysis is necessary to weed out those cases of lymphosarcoma showing the homogeneous protein simulating M-protein. Its reduced avidity to lipid staining is helpful in this respect. Such a homogeneous γ-globulin fraction has also been seen in a case of acute erythremic myelosis.

Other than the recently reported [182] transplantable myeloma tumors in mice which show an M-type protein roughly correlated in quantity to the size of the tumor, only one other animal shows such a paraprotein. This is the parakeet. This bird has a high incidence of primary pituitary tumors which are easily transplanted. Within four days from the time of transplantation, a paraprotein appears in their serum representing 50% to 65% of their total serum proteins. It will disappear if the tumor is completely removed.[179-181] Such experimental animals offer models to understand more fully these qualitatively abnormal proteins.

Hodgkin's disease is unique among the lymphomas, as the occurrence of hypogammaglobulinemia is so rare and when seen usually appears only in the terminal stage of the disease. In contrast, patients with lymphosarcoma may show this protein de-

ficiency years before the clinical diagnosis is made. The main advantage of serum protein electrophoresis in Hodgkin's disease would appear to be as an aid in determining whether the disease is active or inactive as a response to treatment. In any chronic disease which may be treated successfully with the disappearance of the signs and symptoms of active disease, the clinical problem arises as to when the condition is reactivated, requiring a search for a focus of activity and administration of additional treatment. The serial electrophoresis of serum proteins on each follow-up visit of the Hodgkin's patient will demonstrate the earliest sign of reactivation of this disease. Over a period of five years, 169 patients with Hodgkin's disease have been followed by serial electrophoresis of their serum proteins (820 samples). The changes characteristic of activity of the disease are (1) decreases of albumin, (2) significant increase in α_2-globulin, and (3) decrease and "splitting" of β-globulin. The earliest change is a gradual increase in α_2-globulin and is, in the absence of secondary infection, correlated well with reactivation of the disease, anticipating clinical evidence as much as six months in some cases. With successful treatment these changes revert to normal levels and the γ_2-globulin may rise in the ensuing months. Gamma$_2$-globulin may, however, increase in the face of continuous activity of the disease. The erythrocyte sedimentation rate commonly used as a guide in these cases is of limited use, as the rise in γ-globulin seen in some successfully treated cases may persist for years, causing an accelerated sedimentation rate but failing as a guide to activity of Hodgkin's disease. Such elevated sedimentation rates are also seen in arrested rheumatic fever, owing entirely to γ-globulin elevation. Serial electrophoretic observations of the serum of Hodgkin's patients is also a more sensitive index of reactivation of the disease than the C-reactive protein reaction. Elevation of the α_2-globulin in these patients may occur as long as six months before clinical evidence of reactivation is found. This phenomenon of "anticipation" may be extremely helpful to the clinician in making an "all-out" attempt to find the site of the Hodgkin's activity and institute prompt therapy.

Reticulum-cell sarcoma in our small series of 27 patients shows serum protein changes paralleling those of lymphosarcoma rather than Hodgkin's disease but with an incidence and severity of hypogammaglobulinemia less striking than lymphosarcoma.

Our reported series of observations are essentially in agreement with the bulk of findings reported by others in the acute and chronic leukemia and the lymphomas.[119-178]

Other reticuloendothelial system diseases show a low sporadic incidence of hypogammaglobulinemia. We have observed this in acquired hemolytic anemia (three cases), idiopathic thrombocytopenic purpura (two cases, one having agammaglobulinemia for two years before the onset of idiopathic thrombocytopenic purpura), aplastic anemia (two cases), and polycythemia rubra vera (one case). Nine cases of classical hemophilia and five cases of thromboplastic-plasma-component-deficiency disease (Christmas disease) have shown only nonspecific changes on serum protein electrophoresis. Bernfeld et al.[281] has reported a characteristic abnormal component in the serum of classical hemophiliac patients, but possibly through limitations of technique I have not seen this. I have been struck by the hypergammaglobulinemia seen in acquired hemolytic anemia and in anaphylactoid purpura in adults. Christenson[288] and Charbonnier[287] have noted γ-globulin increase with hemolytic anemia associated with cold agglutinins.

Multiple myeloma[183-217] is unique in that this is one disease associated with the synthesis of a qualitatively abnormal serum protein (paraprotein). Sequential amino acid assay,[198] as well as immunochemical studies[212,217] on isolated myeloma proteins, has shown the *qualitative* differences between these proteins and normal γ-globulin.

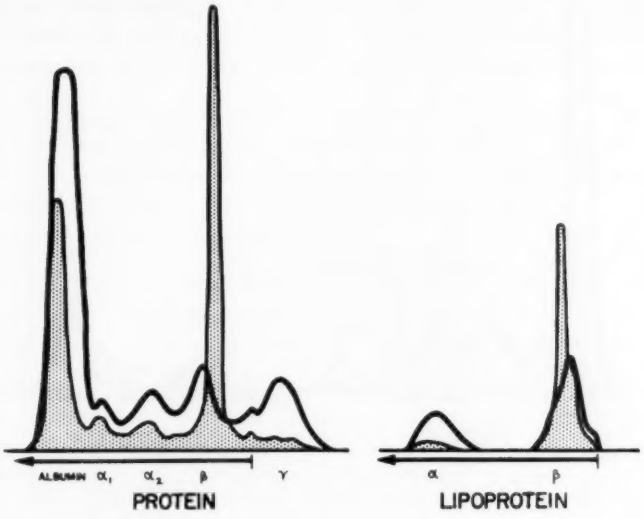


Fig. 14.—Myeloma, β-type. The narrow band of homogeneous M-protein is seen in the β-area. This component also shows an affinity for lipid stain. Gamma-globulin is markedly decreased, as are all other components to a smaller degree. This M-protein was a macroglobulin with a sedimentation constant over 19.

Myeloma protein is also unique in that evidence would suggest that the protein differs qualitatively between myeloma patients but in a given myeloma patient is constantly reproduced throughout the course of the patient's disease. This individual qualitative difference in M-proteins in myeloma patients has also been demonstrated in Bence Jones urinary protein among a group of myeloma patients.[215] M-protein on electrophoretic analysis is characteristically homogeneous, appearing as a narrow densely staining band. Heterogeneity constants calculated in this laboratory on fractionated normal γ-globulin have been 0.205 10^{-5} cm.^{2} sec.$^{-1}$ volt^{-1}, in contrast to similarly fractionated M-protein with constants of 0.017 10^{-5} cm.^{2} sec.$^{-1}$ volt^{-1}, attesting to the marked homogeneity of M-protein.

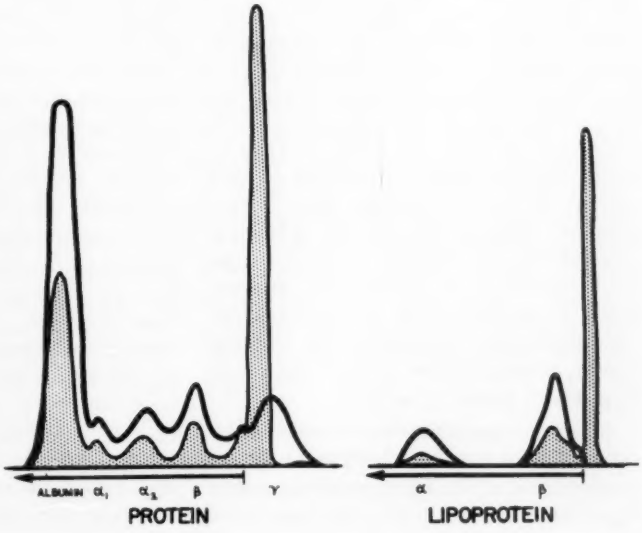


Fig. 15.—Myeloma, γ-type, showing M-protein in γ-area. Note the affinity of lipid stain for the M-protein, the marked decrease of γ-globulin, and the decrease of other components.

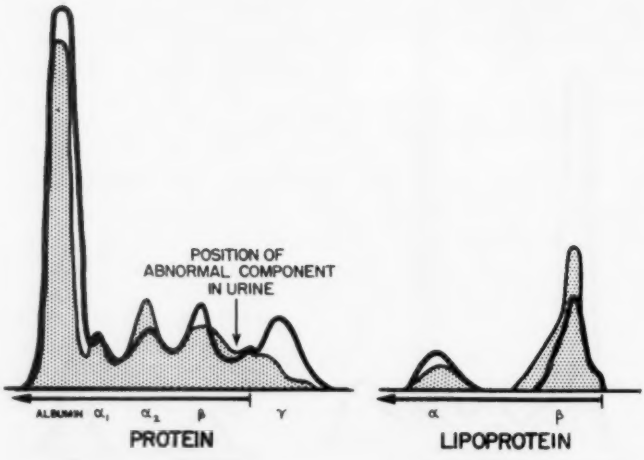


Fig. 16.—Myeloma with no M-protein demonstrable in serum; severe renal impairment; Bence Jones protein not found in urine; M-protein found in urine. Note decrease in γ-globulin and shift of β-lipoproteins into α_2-position as seen in nephrotic syndrome.

Sixty-two cases of myeloma (twenty-eight females, thirty-four males) whose serum was examined by paper electrophoresis in this laboratory showed that the M-protein in six cases (10%) migrates in the β-area (Fig. 14); fifty patients (80%), in the γ-area (Fig. 15), and six (10%) showed no M-protein. Of those migrating in the γ-area, 23 migrated with a fast electrophoretic mobility and 27 migrated as slow-moving γ-globulin. Of the six cases that showed no M-protein in their serum, all showed hypogammaglobulinemia, and in three of these cases M-protein (not Bence Jones protein) could be demonstrated in large quantities in their urine (Fig. 16). I have not been privileged to examine the serum of a patient with M-protein in the α-area. If a group of myeloma patients' serum are examined, the mobility of their various M-proteins actually form a spectrum of mobilities from β- to slow-moving γ-mobility areas. Another important finding in the serum of all patients with myeloma is the virtual absence of normal γ-globulin. This finding may account for the immunologic paralysis of these patients when challenged with potent antigens.

All of the patients with myeloma whose serum showed M-protein (55 cases) showed a component of the same mobility as their M-protein staining densely with lipoprotein stain (Sudan black B). Whether this is evidence of a lipid component in M-protein or merely a marked avidity for the nonspecific absorption of the lipid dye remains to be seen. Quantities of normal γ-globulin similar to M-protein do not demonstrate this lipid staining, nor in my experience has the homogeneous γ-globulin component, seen rarely in some other reticuloendothelial diseases, e. g., lymphosarcoma.

If electrophoretic patterns are performed on the serum of myeloma patients and stained for carbohydrate-linked proteins, the M-protein band also has an affinity for this dye reaction. In three of the patients in our series this was done and a distinct band was observed. This finding was reported originally by Sachs,[207] Rice,[208] and Tropeano.[216] However, in our hands this staining reaction has not been satisfactory as regards reproducibility.

In repeated observations on our 61 cases throughout the course of their disease, none have shown a decrease or disappearance of their M-protein. If the terminal nephrotic stage of the disease appears, the characteristic serum protein changes of nephrotic syndrome are superimposed on the previous pattern of myeloma. One female, well studied in three clinics over a three-year period and diagnosed by all as classical lupus erythematosis, then developed myeloma,

from which she died. Multiple L. E.-cell preparations were negative as her myeloma developed and progressed to her eventual death.

One case of *macroglobulinemia* occurring in a Negro with myeloma showed an M-protein migrating in the β-area. Ultracentrifugation of this isolated protein showed it to have a sedimentation constant of S19, attesting to its macromolecular nature. It is of interest that a water-dilution test of this serum was negative. Macroglobulinemia, i. e., the presence of a serum protein of extremely high molecular weight, has been observed most frequently in myeloma but has also been observed in lymphosarcoma, chronic lymphatic leukemia, "atypical lymphatic hyperplasia," [225] lupus erythematosis,[232] nephrosis,[232] carcinoma of the uterus,[245] congenital syphilis,[249] and Sjögren's syndrome [253] and may occur in the absence of these findings as a hemorrhagic syndrome "Waldenström's macroglobulinemia," a primary disease syndrome.[220,231-233, 241,243,244,246-248,250,254] This protein when present in significant quantity simulates M-protein of myeloma in serum electrophoresis. Its differentiation from M-protein can be made only by optical ultracentrifugation. The simple water-dilution test is not satisfactory for its identification. Also, the diagnosis of the syndrome of Waldenström's macroglobulinemia can be made only by the exclusion of multiple myeloma and other diseases of the reticuloendothelial system as a primary diagnosis. The diagnosis of myeloma remains a tissue diagnosis. Recent work [222] has suggested that macroglobulins may actually be polymers of M-protein or normal γ-globulin capable of being hydrolyzed to proteins of smaller molecular weight (S6-7) in the range of M-protein and normal γ-globulin and may be immunologically identical to normal γ-globulin,[254] although this is questioned by others.[218]

Cryoglobulins are proteins which precipitate at temperatures below 37 C, usually at 4-20 C. When present in serum they cause a gel formation at 4 C which is reversible at 37 C. This gel-sol phenomenon can be carried out indefinitely. Cryoglobulins have been reported in alcoholic or nutritional cirrhosis,[237] rarely in Raynaud's syndrome (not in this laboratory),[224] myeloma,[228] chronic lymphatic leukemia,[224,226,234] lymphosarcoma,[223] cancer,[227] and as an isolated finding.[229,238,239,251] A closely related phenomenon is *cryofibrinogenemia*.[235,236] This has been seen in two myeloma patients in this laboratory and is characterized by gelling of the serum at 4 C with return to liquid form at 37 C but on repeat cooling and warming at 37 C forms an insoluble precipitate of fibrinogen after which the gel-sol phenomenon is no longer obtainable. This has been observed in isolated Fraction I of Cohn and may be related to normal-occurring cold insoluble globulin present in these pathologic states in increased amounts. If electrophoretic analysis is routinely carried out in a refrigerated room, cryoglobulins will appear as a precipitate of dense staining quality at the point of application of the sample, showing no migration in the electrical field.

Pyroglobulins, that is, protein-precipitated or gelled by heat, is best characterized by Bence Jones protein which in urine is insoluble at 50-60 C and becomes soluble at 100 C. Rarely a patient with myeloma will have sufficient Bence Jones protein in the serum to cause gelling of the serum at 60 C. Recently such a patient was seen whose diagnosis was suspected when a sample of serum was incubated in a water bath at 60 C for inactivation of complement in preparation for performing a Wasserman test. On more careful examination, this gel formed at 20 minutes' incubation at 40 C and in 10 minutes at 60 C. He was otherwise a classical myeloma of a slow γ-type, with Bence Jones proteinuria and characteristic dense bone marrow infiltration with abnormal plasma cells.

"Agammaglobulinemia" and Hypogammaglobulinemia

Deficiency to virtual absence of γ-globulin is seen in a group of clinical entities whose

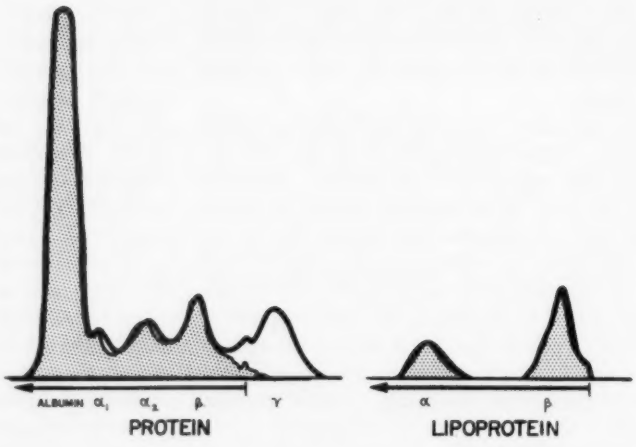


Fig. 17. — Agammaglobulinemia in an adult. This serum sample was taken when the patient had no clinical evidence of infection. The patient had previously had repeated pneumococcic pneumonia and later idiopathic thrombocytopenic purpura with successful splenectomy.

evaluation can best be made by electrophoresis. It is true that the apparent complete absence of γ-globulin can be defined with greater exactitude by immunochemical methods, but the original observation of decreased γ-globulin can best be determined by simple zone electrophoresis. Bruton's [255] original contribution correlating the clinical picture of a child with multiple infections and apparent immunological paralysis with absent serum γ-globulin was quickly followed by many reports by Janeway, Good, and others.[255-280] The first report of this entity in an adult was to my knowledge in a popular lay magazine [272] by a patient studied in a series of West Coast Veterans' Hospitals and was quickly followed by multiple reports of similar cases in legitimate medical journals (Fig. 17).[256,257,261,263,274,277] Attention has also been called to the occurrence of hypogammaglobulinemia in other primary diseases of the reticuloendothelial system,[149,262] primarily of lymphatic origin.[134,175,140]

The significance of a third group of juveniles having transient hypogammaglobulinemia must be considered in relation to the levels of γ-globulin known to be lower in this age group than in the adults.

The serum electrophoretic pattern in agammaglobulinemia patients should, in the absence of infection, show normal albumin and α-globulins and frequently decreased β-globulin [273] and absent γ-globulin. Most patterns will show some detectable γ-globulin as a faint-staining "tail." Alpha- and beta-lipoproteins appear normal. When infection occurs in such patients the nonspecific changes of decreased albumin, increased α_2-globulin, and further decrease and splitting of β-globulin may occur. A clinician should not expect to see a detectable increase in γ-globulin on electrophoresis following intramuscular injections of therapeutic γ-globulin, despite the obvious clinical value obtained. The electrophoretic method is usually too gross for such fine changes. An excellent review of this subject has been made by Janeway and Gitlin.[279]

Diseases of the Kidney

Serum proteins are lost as proteinuria in renal disease and therefore would be expected to produce significant changes in the serum electrophoretic pattern.

Acute pyelitis (five cases) causes no diagnostic changes in the serum electrophoretic pattern. Elevation of α_2-globulin and minor decrease in albumin is seen but is nonspecifically seen in infections of all kinds. Similarly, *acute hemorrhagic nephritis* [298] (four cases) shows the same nonspecific changes. However, when this disease is severe, albumin may be reduced as much

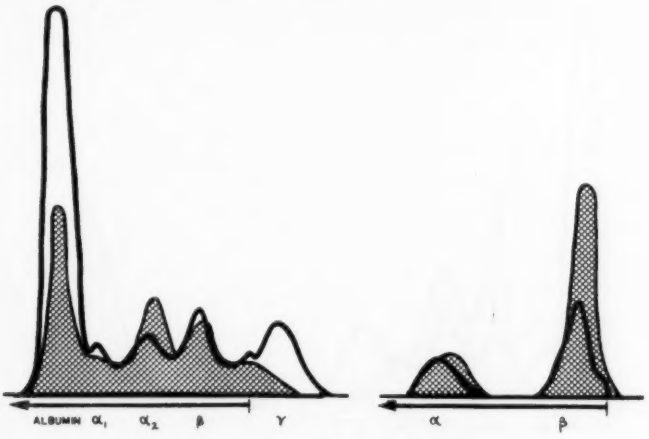


Fig. 18.—Anaphylactoid purpura (Henoch-Schönlein type) with hemorrhagic nephritis. Note pattern similar to nephrotic syndrome (Fig. 20).

as 80% from normal levels and α_2-globulin may be increased up to three times normal levels. One interesting case of anaphylactoid purpura of the Henoch-Schönlein type seen in a girl, characterized by hematuria, proteinuria, ecchymoses of the skin, and arthralgia, demonstrated the difficulty of differentiating this disease from acute hemorrhagic nephritis of streptococcal origin. A marked hypoalbuminemia was seen with elevation of α_2- and β-globulins, hypogammaglobulinemia, and a striking increase in β-lipoprotein, with no α_2-shift. On conservative management, the child improved with a reversal of the electrophoretic pattern toward normal, except for a persistence of the elevated β-lipoprotein (Figs. 18 and 19). *Chronic pyelonephritis* and *chronic glomerulonephritis*[303] (22 cases) show nonspecific changes, as seen in chronic infectious diseases with normal or moderately decreased albumin and normal or elevated α_2-globulin, and in one-half of these cases significant elevation of γ-globulin is seen.

Nephrotic syndrome[291-297,299-302,304-306] (37 cases), regardless of its etiology, has a diagnostic serum electrophoresis pattern. One of the earliest applications of Tiselius electrophoresis was in this disease.[291] Albumin is markedly reduced to the lowest levels seen in any disease; α_1-globulin is reduced; α_2-globulin is elevated three to four times

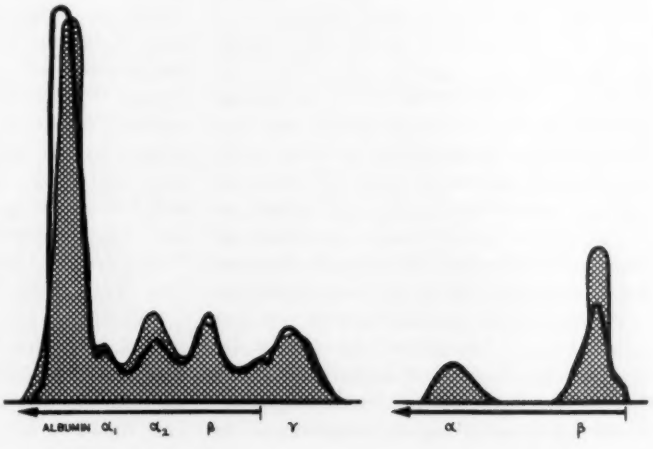


Fig. 19.—Same patient as Figure 18, nine weeks later. Note minor nonspecific changes but with persistent increase in β-lipoprotein.

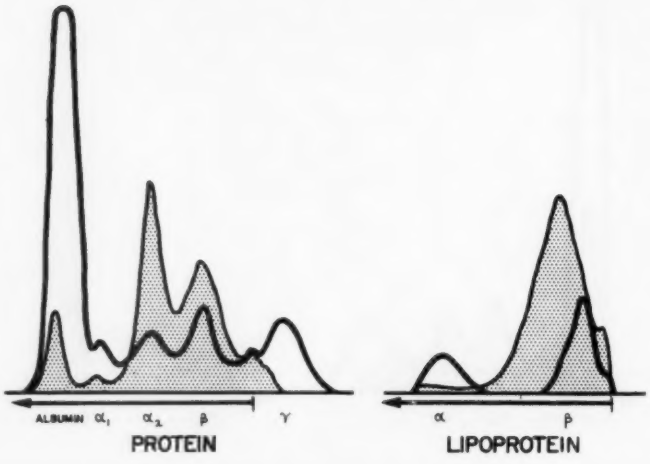


Fig. 20. — Nephrotic syndrome in a child. Note marked decrease of albumin and α_1- and γ-globulins, increase of α_2- and β-globulin, increase of β-lipoprotein with "α_2-shift" (serum sample provided by Dr. Warren Wheeler, Children's Hospital, Columbus, Ohio).

normal levels and frequently fused with β-globulin to make their individual quantitations difficult; γ-globulin is decreased to extremely low levels; α-lipoprotein is decreased in most cases, and β-lipoprotein is increased far above normal levels. The latter finding is accompanied by the appearance of lipid staining in the area of α_2-globulin. This "α_2-shift" of lipids has been seen in lipid nephrosis of childhood (Fig. 20), in nephrotic syndrome of chronic glomerulonephritis, in nephrotic syndrome of diabetes mellitus (Kimmelstiel-Wilson's disease), in amyloid disease of the kidney, and in a somewhat modified state in the nephrotic stage of multiple myeloma. Whether this α_2-lipoprotein represents a different lipoprotein of nephrosis or change in electrophoretic mobility of modified β-lipoprotein is not known. I do not believe that this is an artifact, as it has not been seen in other disease states characterized by elevated β-lipoprotein, such as essential lipemia, myxedema, generalized cholesteatomas, or the severe lipemia seen rarely in some mild diabetics. Two cases of severe nephrocalcinosis, one with a proven parathyroid adenoma, showed the "α_2-shift" changes of lipoproteins but without the other striking protein changes of nephrosis. Minor "α_2-lipoprotein shifts" have been seen in the third trimester of normal pregnancies. In patients with chronic renal disease (chronic pyelo- or glomerulonephritis) who have been followed by serial electrophoretic analysis, characteristic serum protein changes of the nephrotic syndrome may occur before the clinical picture would warrant this diagnosis. Chronic renal insufficiency with *uremia* has been reported by Finkle[307] to show nonspecific changes of α_2-globulins which have on serial observations shown good correlation with changes in functional impairment of renal parenchyma.

Collagen Diseases

One case of *primary amyloidosis* showed nonspecific changes as well as a curious elevation of a fast-moving γ-globulin (Fig. 21). Excellent studies of electrophoresis in this problem are reported by Block[441] and Lezgus.[445] The changes observed in *Boeck's sarcoid*[443] were entirely nonspecific and not related to the sites of involvement, e. g., liver and lung. Elevated γ-globulin was noted in all except 2 of the 12 cases studied. *Disseminated lupus erythematosis*[329, 331-334] produced no specific changes (Fig. 22). The notable heterogeneous increase in γ-globulin has been previously investigated on isolated γ-globulin fractions in this laboratory by physiochemical methods (boundary elctrophoresis and ultracentrifugation) and found to be similar to γ-globulin ob-

Collagen Disease

Disease	Cases, No.	Albumin			α_1-Globulin		α_2-Globulin		β-Globulin			γ-Globulin		α-Lipoprotein		β-Lipoprotein	
		N	Slight ↓	Severe ↓	N	↑	N	↑	N	↑	Split ↓	N	↑	N	↑	N	↑
Amyloidosis	1		1			1		1			1		1	1		1	
Boeck's sarcoid	12	3	7	2	6	5	1	4	7	1	3	7	4	4	1	11	10		2	8	3	1
Disseminated lupus erythematosus	13	4	4	5	7	6		3	8	2	4	1	3	5	4	9	11		2	5	6	2
Rheumatoid arthritis	33	13	11	9	23	10		8	23	2	17	4	4	8	6	27	32		1	16	15	2
Polyarteritis nodosa	2			2		2			2			1		1	1	1	1		1	1	1	
Osteoarthritis	9	4	4	1	7	2		4	4	1	6	1	2		5	4	9			6	3	1
Fibrositis	3	2	1		2	1		1	2		1			2	3		3			1	1	1
Scleroderma	7	1	5	1	6		1	1	5	1	2			2	3	1	6	7		4	2	1
"Lupoid hepatitis"	1			1		1				1				1	1		1	1			1	
Thrombotic thrombocytopenic purpura	2			2	2			2							2		2	2		1	1	
Dermatomyositis	2			2			2			2					2		2	2				2

tained from pools of normal human plasma. Such studies obviously do not prove identity of proteins, merely similar physical characteristics. The serum electrophoretic changes seen in *rheumatoid arthritis*[308-328,338] are nonspecific and not, in our 33 cases, related to other nonspecific "rheumatoid arthritis serology tests." These nonspecific changes include α_2-globulin and γ-globulin increase. Serial observations of the serum electrophoretic patterns would appear to show good correlation with the presence or absence of the active disease process. The relationship of serum electrophoretic changes to the latex-fixation test has been reported.[330] The seven cases of *scleroderma*[428,430] showed no specific changes, including three cases who had *Raynaud's syndrome*. A search for cryoglobulins in the three latter cases was negative. One young female with *thrombotic thrombocytopenic purpura* was followed by serial electrophoretic analyses of her serum proteins for 17 days prior to death and showed only nonspecific changes.

Two females with *dermatomyositis* showed very similar patterns on repeated serum examinations, characterized by a marked decrease in albumin (40% to 50%); decreased α_1-, α_2-, and β-globulins; an increase in γ-globulin (primarily γ_2), and a decrease in α- and β-lipoproteins. This type of pattern is similar to that seen in hepatic parenchymal disease; however, both of these patients showed normal liver function by conventional tests as well as liver biopsy.

Infectious Diseases

In our experience and that of the published results of others, with many forms of specific bacterial, viral, and fungal diseases, no changes specific for infectious diseases have been observed by the electrophoretic analysis of serum proteins. However, important changes of a nonspecific nature occur in a rather reproducible sequence regardless of the infectious agent. These changes are those referred to as a "stress pattern," as seen in many febrile states and conditions characterized by tissue breakdown,

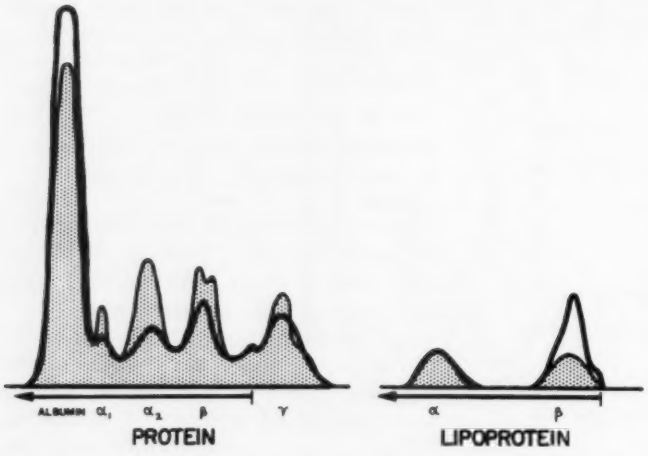


Fig. 21. — Primary amyloidosis. Note nonspecific changes of albumin and α_1-, α_2-, and β-globulins, increase in γ_1-globulin of questionable significance, and decreased β-lipoprotein.

such as malignancy. The changes are a variable decrease in albumin; normal or elevated α_1-globulin; increase in α_2-globulin (the commonest single change); decrease and "splitting" of β-globulin, and heterogeneous increase in γ-globulin, rarely γ_2 alone and variable transient changes in the quantity of α- and β-lipoproteins.

That such variations from the normal serum electrophoretic pattern may occur primarily as a response to fever is suggested by the observations in this laboratory for two years on three members of a family representing three generations, with repeated *familial periodic fever,* whose patterns showed persistent hypergammaglobulinemia, with an increase in α_2-globulin during each of their febrile periods, returning to normal with the disappearance of the fever.

A study now in progress of experimental infections in man, to date with over 900 serial serum samples subjected to electrophoretic analysis, has afforded an opportunity to observe the sequence of serum protein changes related to infection alone.[344] The initial event after bacterial invasion was an increase in α_2-globulin and a minor decrease in albumin (10% to 15%), followed over a period of days to weeks in

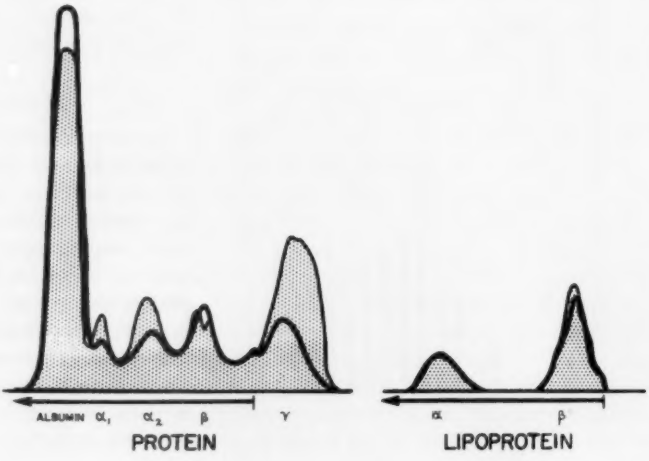


Fig. 22. — Disseminated lupus erythematosus. Note minor changes of albumin and α- and β-globulins and large increase in γ-globulin.

some cases with a gradual rise in γ-globulin. In severe forms of the infection, these findings were magnified and β-globulin decreased and split into β_1- and β_2-globulin. With clinical resolution of the infection these changes reverted to normal. A curious, as yet unexplained, observation has been made. As α_2-globulin increases in response to active infection and reaches its apex, then or a few days later γ-globulin may decrease, in some cases quite significantly, and may remain lower than control levels for weeks despite adequate clinical response to the infection. This change in our laboratory is referred to as "α_2- γ-reciprocity." Details of this study will be reported subsequently. Again this would stress the importance of serial electrophoretic observations on an individual patient.

Other *acute infections* that are self-limiting or respond to specific antibacterial agents show the nonspecific changes described. These diseases include lobar pneumonia (two cases); infectious mononucleosis (eight cases); acute upper respiratory infections, probably viral (eight cases); viral pneumonia (five cases); brain abscess (two cases); appendiceal abscess (three cases); parotitis (two cases); meningitis (four cases); prostatitis (four cases), and sinusitis (five cases).

Subacute and *chronic infections*, especially if suppuration is a prominent finding, show exaggeration of the albumin deficiency and hypergammaglobulinemia. Such diseases as bronchiectasis (nine cases), tuberculosis (eight cases), lymphopathia venereum (three cases), chronic osteomyelitis (two cases), chronic otitis media (two cases), histoplasmosis (four cases), actinomycosis (two cases), and blastomycosis (one case) are examples. Of two cases of staphylococcal subacute bacterial endocarditis, one showed a gradual increase of a homogeneous γ_2-globulin that had no avidity for lipid stains.

Reports of electrophoresis of serum proteins in a variety of infectious disease states would tend to verify the nonspecific dysproteinemia that is produced by practically any infectious agent. These include infections in general,[355,356,384] typhus,[339] rheumatic fever,[340,341,366,370,371,376] lymphogranuloma venereum,[342,382] tuberculosis,[343,347,352,353,358-360,377,380] leprosy,[345,346,364,365,372,374,387] leishmaniasis,[348,389] syphilis,[349,354,367,373] pinta and yaws,[350] malaria,[351,379] pneumococcic infections,[357] smallpox,[361] infantile gastroenteritis,[362] diphtheria and scarlet fever,[363,383] poliomyelitis,[368,369,375,381] infectious mononucleosis,[378] Q-fever,[385] toxoplasmosis,[386] and typhoid fever.[388]

Diseases of the Endocrine Glands

Cushing's disease[397] in two patients, caused by an adenomata of the adrenal in one and cortical hypertrophy in the other, showed no change in serum proteins except an elevation of α_2-globulin. Five patients with *nontoxic goiters* showed no changes that could not be accounted for by their primary disease and when occurring as the only finding produced no electrophoretic change in serum proteins. *Hyperthyroidism*[394] (14 cases) showed elevation of α_2-globulin in 5 cases, either splitting or decrease of β-globulin in 6 instances, and decreased β-lipoproteins in 6 of the cases. One case who was pregnant at the time showed an elevation of β-lipoprotein, as did another case who demonstrated *pretibial myxedema*. For an unexplained reason 4 cases out of the 14 showed only 50% of normal γ-globulin levels. It is interesting to speculate on this finding in view of the known lymphocytosis in this disease and the fact that the highest incidence of hypogammaglobulinemia occurs in chronic lymphatic leukemia and lymphosarcoma, both affecting normal lymphocytic production. Of 12 cases of *hypothyroidism*,[393,395] 4 showed frank myxedema. The serum protein changes were minimal except for four instances of considerable hypergammaglobulinemia. However, β-lipoproteins were markedly elevated in the four myxedema cases with no significant "α_2-shift," as seen in nephrotic syndrome, and elevated to a

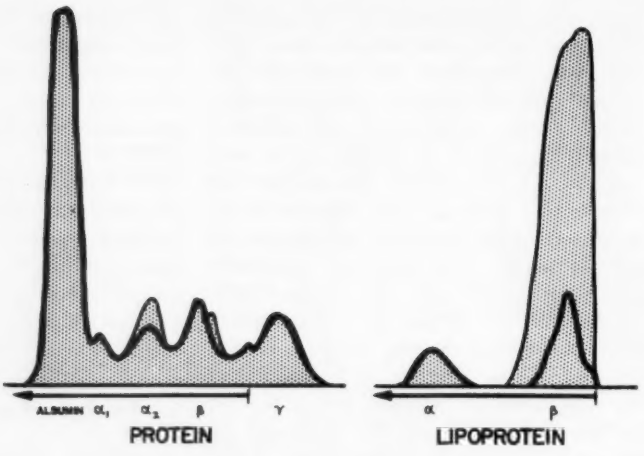


Fig. 23. — Myxedema. Note minor abnormalities of proteins, with marked increase in β-lipoprotein. Radioactive iodine uptake less than 5%.

smaller degree in four other cases of less severe hypothyroidism, roughly correlated with blood cholesterol levels (Fig. 23). One poorly understood case with a considerable degree of hypothyroidism showed a normal β-lipoprotein, thought possibly to be accounted for by concomitant hepatic disease. The diagnostic significance of a marked elevation of β-lipoprotein in this disease despite normal or near-normal serum proteins is noted, as such a finding has been found only in *essential hyperlipemia* (two cases), *multiple cholesteatomas* (two cases), and *familial hypercholesterolemia* (one family of three patients). One case of *acute thyroiditis*[398,399] showed albumin reduced 25%, α_1-globulin increased 2.5 times normal, α_2-globulin increased 3.7 times normal, a split of β-globulin, γ-globulin increased twice normal, and a significant increase of β-lipoprotein. These findings are nonspecific and agree with more recent reports by others.[398,399] One patient with ovarian agenesis showed normal serum proteins and a slight increase in β-lipoprotein, and one *eunuch* on testosterone therapy showed an increase of α_2-, β-, and γ-globulins and a decrease of β-lipoprotein. Three cases of *panhypopituitarism* showed nonspecific protein changes, and one had an elevated β-lipoprotein. One patient with acquired hemolytic anemia and diabetes mellitus followed months later by diabetes insipidus and panhypopituitarism showed an elevated γ-globulin, a decrease in albumin, α- and β-globulins, and a virtual absence of β-lipoprotein. No autopsy was obtained in this case.

Of 221 cases of *diabetes mellitus*[390-392] whose serum was examined electrophoretically, 110 were from our outpatient clinic and 111 were hospitalized because of some complication of their disease or some secondary disease. Normal levels of albumin were found in 77% of the outpatient diabetics and only 29% of those hospitalized. Of those showing severely decreased albumin (30% or more decreased from normal), only 5% were from the outpatient group, merely suggesting that the severer diabetics requiring hospitalization had more significant hypoalbuminemia.

Alpha$_2$-globulin was elevated in 58% of the diabetic patients and decreased in 3% and was not related particularly to the severity of the disease except where nephrotic syndrome occurred.

Beta-globulin was increased in 13%, decreased in 13%, "split" in 7%, and showed a diffuse spreading band in 10%, the latter usually seen in patients whose beta-lipoproteins were significantly increased. Gamma-globulin was elevated in 40% and decreased in 10%, the latter group having long-stand-

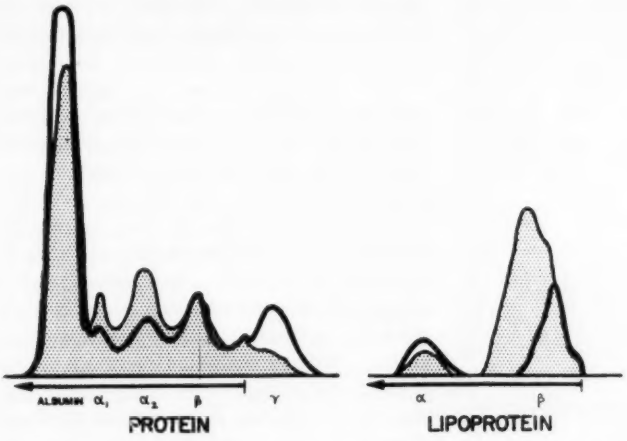


Fig. 24.—Diabetes mellitus with nephrotic (Kimmelstiel-Wilson) syndrome. Note decreased albumin, increased α_1- and α_2-globulin, normal β-globulin, decreased γ-globulin, marked increase of β-lipoprotein, with "α_2-shift."

ing degenerative vascular disease and proteinuria. Alpha-lipoproteins were not significantly altered in this group of patients. Beta-lipoproteins were decreased in 3% of the patients and increased in 64%, and all but 6 patients of these 141 cases showed some degree of "alpha$_2$-shift" (Fig. 24). The latter findings of "α_2-shift" with elevated β-lipoproteins is seen in the nephrotic syndrome and in some normal pregnant women. Such a shift of β-lipoproteins was described by Blöch and Graf [391] as related to diabetic acidosis. Attempts to correlate (with Dr. George Hamwi of the Department of Endocrinology) the levels of blood cholesterol, blood urea nitrogen, evaluation of the degree of retinopathy, and renal function in 120 of these diabetic patients with elevation of β-lipoprotein and α_2-shift were unsuccessful. One autopsied case showed typical histiologic changes of intercapillary glomerular sclerosis but had shown normal β-lipoproteins. The author therefore believes that while the typical serum protein and lipoprotein changes of the nephrotic syndrome are present in most nephrotic syndromes, diabetic intercapillary glomerulosclerosis may be present rarely without the presence of these serum protein changes.

Diseases of Heart and Blood Vessels [400-415]

Rheumatic and arteriosclerotic valvular heart disease in 43 hospitalized patients produced significant hypoalbuminemia in over half the patients (65%) and increased amounts of γ-globulin in 50% in the same population. Beta-lipoprotein was elevated in 20% of this group of patients over control levels, but when correlated with age as a control did not appear significantly increased. Thirty-one patients with *essential hypertension* [415] showed hypoalbuminemia in one-third of their number, increased γ-globulin in one-half of the patients, and increased amounts of β-lipoprotein in 50%, probably of significance over the relation of age alone. This latter finding is of interest, but admittedly quantitation of lipoprotein by this method is subject to considerable error even with the closest of controls. Four young patients with *myocardial infarction* [401,405,407,408,410] showed nonspecific protein changes related to their acute disease and significantly increased β-lipoproteins in two, one of whom had a familial hypercholesterolemia. One case of acute coronary occlusion in an elderly adult showed only nonspecific increase of α_2-globulin of a transient nature. Dangerfield and Smith [410] have reported on α_2-lipoprotein shift in over 50% of their myocardial infarction patients. *Pericarditis* (six patients) produced only those nonspecific changes as seen in a stress pattern. One of these cases resulted from mediastinal x-ray therapy for Hodgkin's disease where

the stress pattern was already present and merely accentuated these findings. *Thrombophlebitis* (nine cases) produced only minor nonspecific changes. *Idiopathic cardiac hypertrophy* diagnosed in two carefully studied cases produced no electrophoretic pattern changes. *Congestive heart failure* with hepatomegaly has produced some transient changes in the pattern simulating the pattern seen in true hepatoparenchymal disease.[409] The relation of lipoproteins to arteriosclerosis [411,413,414] is beyond the scope of this paper and my investigational experience.

Diseases of Nervous System

Four cases of *epilepsy* (one petit mal, three grand mal) showed nonspecific changes of decreased β-globulin and a slight increase in α-globulin in two cases. One *chromophobe adenoma* of the pituitary showed a split of α_2-globulin, and one case of *diabetes insipidus* showed a twofold increase in α-globulin. *Herniated nucleus pulposus* (three cases) and *extradural vascular anomaly* (one case) produced no dysproteinemia. One case of *schizophrenia* showed a normal serum protein pattern.

Of special interest was the serum electrophoretic pattern in patients believed to have *psychoneurosis*, where 10 out of 15 cases showed entirely normal patterns and the other 5 showed only very minor nonspecific changes. The finding of a normal serum electrophoretic pattern in such cases has been of additional diagnostic comfort to me.

Zinneman and Rotstein [416] have reported significant hypogammaglobulinemia in 9 out of 12 patients with *dystrophia myotonia*. A γ-globulin increase was noted on antigenic stimulation of these patients. Saifer and associates [419,420] and Bernsohn [418] have reported serum electrophoretic changes in *multiple sclerosis* which would, however, seem to be nonspecific.

Diseases of the Skin [424-431]

Five patients with *atopic dermatitis* showed only minor deviations from the normal serum electrophoretic pattern. *Drug allergy* produced a marked increase in heterogeneous γ-globulin in one patient with a severe penicillin sensitivity. Two other patients having a similar sensitivity showed only minor changes in their serum proteins. One severe case of *acne rosacea* showed a significant elevation of β-lipoprotein very possibly unrelated to this disease. *Cellulitis* in two patients showed the nonspecific changes of α_2- and β-globulins as seen in infections, with a return to a normal pattern in one case two months later. One case of *erythema nodosum* (primary disease unknown) showed only an increase in α_2-globulin as a nonspecific change, and one case of *exfolliative dermatitis* showed α_2-globulin elevation and β-globulin decrease. Of interest were the normal serum protein patterns seen in four cases of *neurodermatitis* and the nonspecific α_2- and β-globulin changes which occurred in one of these patients who developed secondary infection of the skin lesion.

Cancer [432-434]

The serums of 53 patients with malignancies of many types other than lymphomata were examined electrophoretically. Four cases of *adenocarcinoma of the colon* showed only nonspecific changes of hypoalbuminemia, increased α_1- and α_2-globulin, decreased and split β-globulin, and elevated γ-globulin in all cases. Alpha- and beta-lipoproteins were considerably decreased in these four moderately advanced cases. Nine cases of *bronchogenic carcinoma* [432] showed similar changes. One of these cases also had a typical nephrotic syndrome with the characteristic serum protein changes seen in this disease. One case was of interest in that he showed a homogeneous γ-globulin elevation which had no lipoprotein component to it, as seen in multiple myeloma. This case unfortunately was diagnosed by pleural fluid cytology, and neither surgical biopsy specimen nor autopsy was obtained. A similar homogeneous γ-globulin was seen in one case of *carcinoma of the cervix*, but five other such cases showed only nonspecific changes.

Carcinoma of the breast (six cases), *undifferentiated carcinomas of the neck* (five cases), *carcinoma of the prostate* (three cases), *renal carcinoma* (two cases), *chondrosarcoma* (one case), *metastatic carcinoma to liver* (two cases) and to *vertebrae* (three cases), and *malignant melanoma* (four cases) all showed only nonspecific changes correlated roughly with the degree of involvement and debility of the patient. *Carcinomatosis* (nine cases), as previously mentioned, besides the nonspecific changes of malignancy, showed two instances of hypogammaglobulinemia. This suggests that such a deficiency may be related to overwhelming involvement of the reticuloendothelial system with cancer invasion. Serum protein changes in *carcinoma of the pancreas* (four cases) are of interest in that in the differential diagnosis of jaundice this disease causes minor nonspecific changes in the electrophoretic pattern but none suggestive of hepatocellular disease. The β-lipoproteins were significantly elevated in two of these cases with early obstructive jaundice.

Diseases of the Lungs

Intrinsic bronchial asthma (eight cases) produced no essential change in the serum protein pattern except when complicated by secondary infection. *Bronchitis* (seven cases) routinely produced elevation of α_2-globulin up to twice normal levels, splitting or decrease of β-globulin, and significant increase in γ-globulin in five out of the seven patients. *Bronchiectasis* (nine cases) caused hypoalbuminemia in all cases, reaching 50% of normal in two advanced cases, elevation of α_2-globulin, decrease of β-globulin in three of the cases, and increase in γ-globulin in all cases, three of which were five to six times the normal quantity. Seven cases of *bronchopneumonia* of unknown etiology produced in all cases nonspecific α_2-, β-, and γ-globulin changes. Four cases of *emphysema* and three proven cases of *silicosis* likewise showed only nonspecific protein changes.

Miscellaneous Diseases

One case of acute *porphyria* in an adult showed decreased α_2-globulin and an increase in β- and γ-globulins, with normal lipoproteins. Five cases of *Stevens-Johnson syndrome* (erythema multiforme exudativum) showed nonspecific changes as seen in infectious diseases. One case of *Weber-Christian disease* with bone involvement showed nonspecific changes seen in infectious diseases.[440] One case of *trichinosis* showed only minor nonspecific changes on multiple observations. Three cases of *silicosis*,[442,444,447] proven by pulmonary biopsy, showed only nonspecific changes related most likely to superimposed infection.

Conclusions

The clinical applications of serum electrophoresis by the filter-paper electrophoresis method are reviewed from the experience of this institution. Wherever possible, patients from this institution have been utilized. The world literature on this methodology is mountainous, and I have made no pretense of including all the contributions to this subject, although the bibliography includes many of the more important contributions.

Information derived from serum protein electrophoresis is of most value diagnostically where protein synthesis is impaired (diseases of the liver and reticuloendothelial system) or where protein is lost (renal disease). It is significant in serial observations on these diseases as well as in disease states where nonspecific changes of serum proteins may be well correlated with the clinical course of the disease (infections, lymphomas). Lastly, it may be of importance when the pattern is entirely normal in the evaluation of suspect malingerers or emotionally upset patients as an additional reassurance to the clinician.

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Appendix

The following is the method of performing filter paper electrophoresis of serum.

A. Materials.—Vertical principle cell (Durrum type) with carbon or platinum electrodes and power supply. Barbital (Veronal) buffer, pH 8.6, μ0.05. Filter paper used is Whatmann 3 mm. in form of 10 in.×14.5 in. sheets. Pipettes to deliver 0.01 ml. and strip applicator (Spinco Co.). Drying oven with fan. Shallow pans for dyeing paper. Photoelectric automatic scanning apparatus (Analytrol, Spinco Division, Beckmann Co., California).

B. Method.—Deliver 0.01 ml. serum to strip applicator and carefully deliver this to a premarked (pencil) site midway on the filter paper sheet which has been premoistened with buffer. Such a paper sheet will hold a normal control in duplicate and four patient serums in duplicate. Place the paper on its holder in the electrophoretic cell, cover, and apply 20 ma. for four to five hours. Remove paper on its holder and dry in oven for 15 minutes at 125 C.

The paper is then cut in strips and one of each of the duplicate strips is placed in a bromphenol blue stain bath (0.01% bromphenol blue with 5% zinc sulfate and 5% acetic acid) for at least four hours. Then place in wash Solution A (2% acetic acid) for 10 minutes, repeat washing for two additional 10-minute periods, and then transfer to Solution B (0.5% sodium acetate in 2% acetic acid) for 10 minutes. An alternate method of washing is to substitute Solution C (2% sodium acetate in 10% acetic acid) for Solution B but reduce the time in two minutes. Dry the stained paper at 125 C for 15 minutes. Expose to ammonia fumes continuously prior to scanning.

The duplicate strip is placed in a semi-saturated solution of Sudan black B in 50% ethyl alcohol for three to four hours. Rinse three times in fresh 50% ethyl alcohol until a faint blue tone remains on the background of the paper. Dry in oven at 125 C for 7 to 10 minutes. In practice I have found it more satisfactory to apply 0.02 ml. serum for lipoprotein analysis.

Scanning of normal control and patient serum are recorded on coordinate paper. The patient's serum electrophoretic pattern is therefore interpreted only in relation to the normal pooled control serum pattern.

Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Evolution of Mitral Valve Surgery

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Medicine is not a stable science. The continued progress being made on all sides makes it difficult to choose a point at which one can stop and attempt to evaluate any single procedure. However true this may be, it is also true that any procedure, after prolonged use, is accepted and established as a part of the therapeutic armamentarium before it is completely evaluated. This is true of mitral valve surgery. Although it has been practiced extensively for only 10 years, it has been accepted by many, if not as the "last word" in treatment of mitral stenosis, certainly as a valuable adjunct to such treatment. When a procedure attains this status, one often finds himself complacent about its use and rather wondering in the back of his mind why his predecessors did not see the ease and value of such a procedure. It is in the hope of helping to prevent this sort of thinking that this paper is written.

Early Descriptions of Mitral Stenosis

It is not surprising to learn that mitral stenosis is a problem which has vexed physicians for a number of years. Just how old a problem it is cannot be ascertained. One of the earliest and most lucid descriptions of the symptoms, signs, and pathologic anatomy of mitral stenosis is that of Vieussens,[1] who, in 1715, treated a patient with this illness during his terminal phase and then performed an autopsy on him. He says, "I perceived that the mouth of the left ventricle appeared very small, and that it had an oval oblong shape; and in searching for the cause of such a surprising fact, I discovered that the mitral valves of this ventricle were really bony, and realized that as they became hardened, they would become thickened and rough enough to cause a marked narrowing of the lumen. . . ."

Corvisart,[2] the personal physician of Napoleon, first described the characteristic presystolic thrill of mitral stenosis in 1806. In this same work he also mentioned the narrow pulse pressure and irregularity of the pulse which frequently accompanies this affliction. His succinct but colorful description of right-sided heart failure which also appeared in this work is worth repeating here: ". . . it is necessary that we have a face of a color like ecchymoses, that we have a very marked enlargement of the veins and particularly those of the liver; that the volume of this organ be increased; that breathlessness be marked and of long standing."

Other contributors to the knowledge of the signs and symptoms of mitral stenosis are Laennec,[3] who described the characteristic diastolic and presystolic murmur in 1826; Bertin,[4] who, in 1833, described the

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precordial thrust associated with hypertrophy of the right ventricle, and Graham Steell,[5] who described the murmur of functional pulmonary insufficiency in 1888.

Later investigators have added little else to the diagnosis of mitral stenosis by history and physical examination. Further experience with these findings and the addition of accessory clinical methods may have improved our diagnostic accuracy, although recent investigators[6-9] cast doubt on this. The diagnostic signs with which actual valvular damage as found at surgery are best correlated are those classical signs and symptoms discussed above.

The first area of discussion may be closed then, with the realization that the findings now used in the diagnosis of mitral stenosis are those which have evolved over the past 150 years and that our "modern" methods have done little to improve upon them.

Pathologic Physiology and Natural History

The same Raymond Vieussens quoted above[1] described his conception of the pathologic physiology of mitral stenosis as follows:

> The lumen of the left ventricle being markedly narrowed, and its margin having lost all of its natural suppleness, blood could no more enter freely and abundantly as it should have into the cavity of this ventricle: so that in the beginning the circulation was impaired, it commenced to dilate extraordinarily the pulmonary vein, because the blood remained too long and accumulated in too large an amount. The blood had no longer commenced to make too long a stay in the trunk of this vein than it retarded the course of that in all the blood vessels of the lungs: so that the branches of the pulmonary artery and pulmonary vein extending throughout all the tissue of this organ, were always too full of blood, and consequently so dilated that they compressed the vesicles, interfered with the free entrance of air or prevented it from leaving freely; that is why the patient always breathed with a great deal of difficulty. As the blood thickened considerably in the lung because of its stay in the blood vessels, its serous portion separated little by little and fell into the cavity of the chest.

Little else was added to the understanding of this condition until the "era of McKenzie," at the turn of the 20th century. Sir James McKenzie[10] pointed out that the cardiac residua of rheumatic fever are dual —valvular and myocardial. Following this revelation, human nature being what it is, and McKenzie's stature in cardiology being what it was, the pendulum of medical thinking swung to an extreme. Everyone stressed the factor of myocardial insufficiency while tending to ignore that of valvular damage. Not until the era of cardiac surgery was well begun did this widespread misconception subside.

With the introduction of cardiac catheterization, many facets of the pathologic physiology, which had previously been inferred from clinical and autopsy studies, could readily be demonstrated. The work of Dexter and Gorlin[11-15] remains a classic in this field.

Although right-sided catheterization has been extremely helpful, the progression of mitral valve surgery has made it obvious that the measurements of left heart function made in this manner are not completely satisfactory. Therefore, left-sided catheterization, either transbronchial or percutaneous, has been introduced.[16-22] This method has the advantage of affording one a direct measurement of the pressure gradient and rate of flow across the mitral and aortic valves and of left ventricular output. This method is still in its infancy, but further investigation with it should make clearer the understanding of altered hemodynamics secondary to valvular damage. Another benefit which can be derived from this method is its application in the postoperative evaluation of patients with mitral stenosis. If one has direct measurements of those factors mentioned above—mitral valve flow, left atrial pressure, and left ventricular output—recorded before and after surgery, this offers an opportunity to evaluate the benefits of surgery quantitatively.

The evaluation of the efficacy of mitral valve surgery has been made difficult by the presence of a number of variables. One difficulty has been uniformly noted, how-

ever. This is the absence or near absence of knowledge of the natural history of mitral stenosis in untreated and medically treated patients. In other words, although the results in series of surgically treated cases of mitral stenosis look impressive, there are no adequate controls with which to compare them.

The first reasonably accurate study of the natural history of mitral stenosis was that of Grant.[23] He found 1000 soldiers during World War I with valvular heart disease and followed them for 10 years. Two hundred thirty-eight of these had mitral stenosis. After 10 years he found that 42% of these had died, 34% were worse, and 24% were unchanged. Of those who had "good" or "fair" exercise tolerance at the beginning of the study, 82% survived 10 years. This study has obvious limitations, but it is of value in two respects: 1. It points out that the prognosis is not uniformly poor in patients with mitral stenosis. 2. It offers a hint that one of the best ways of evaluating a patient with mitral stenosis is by determining his exercise tolerance.

The work of Bland and Jones,[24] while affording much helpful data on rheumatic fever and rheumatic heart disease in general, has little to offer in a consideration of mitral stenosis alone. They have followed 1000 children and adolescents from the time of their initial episode of rheumatic fever for 20 years. For purposes of this discussion, one need note only that 117 of these patients developed pure mitral stenosis. Of these 117, only 12 developed evidence of pulmonary hypertension. These authors observe that the presence of the characteristic murmur of mitral stenosis need not necessarily indicate a high degree of narrowing of the mitral orifice. In addition, they note that patients may tolerate mild degrees of mitral stenosis for many years without obvious progression or disability.

One hundred seventy-one cases of mitral stenosis admitted to the Toronto General Hospital from 1937-1941 were studied by Wilson and Greenwood.[25] Of these, 120 died: 50 of congestive heart failure, 11 of pulmonary edema, 17 of emboli, 13 of pulmonary infarction or pneumonia, 9 of bacterial endocarditis, and the remainder of other causes. They found the best indicators of advanced disease to be severe pulmonary congestion, right-sided heart failure, and atrial fibrillation. The average age at onset of severe pulmonary congestion was 40.1 years, 16% of these patients being dead within 6 months. The average age at onset of right heart failure was 42.1 years, 24% of these patients dying within 6 months. Atrial fibrillation had an average age of onset of 43.3 years, and 16% of these patients died within 6 months also. This is obviously a weighted study, since it includes only patients whose symptoms required them to be hospitalized. However, it is useful in helping one to decide which patients require surgery.

G. K. Graham et al. presented a study of the clinical and autopsy findings in 101 cases of mitral stenosis. They found about the same incidence of causes of death as other authors but differed on other points. First of all, they found that the presence of atrial fibrillation did not necessarily indicate severe mitral stenosis. They found that in those patients dying of cardiac causes there was no correlation between the cause of death and the severity of the mitral stenosis. There was good correlation between the presence of right ventricular hypertrophy and the severity of the stenosis. In addition, all patients with severe lung changes had severe mitral stenosis, although the converse was not necessarily true. The conclusions drawn from this study were that the natural history of this disease needs further study and that, on the basis of present knowledge, commissurotomy is not indicated except in patients with incapacitating or progressive symptoms.

By far the best and most exhaustive study of this aspect of mitral stenosis is that of Oleson.[27] He presents 271 patients with mitral stenosis followed from 3 to 20

years without surgery. The average age at death was 47 years. Of patients in Class II (New York Heart Association), 70% survived 20 years or longer. Of patients in Class III with normal sinus rhythm or Class II with atrial fibrillation, 46% survived 10 years or longer. Congestive heart failure was the most ominous symptom, 95% of patients dying within a year after its onset. It is obvious from these figures that it will require many years of close observation and critical evaluation before any really valid conclusions can be drawn concerning the efficacy of mitral valve surgery.

Evolution of Surgical Procedures

"No man who wishes to retain the respect of his colleagues would dare attempt a suture of the heart." So said Bilroth, in 1883, cited by Holman,[28] and so believed the world of surgery until 1902, when Sir Lauder Brunton "threw down the gauntlet to them." A few successful surgical repairs of wounds of the heart plus his own observations of patients at autopsy prompted Sir Lauder, a cardiologist, to suggest surgical correction of mitral stenosis.[29]

The flood of condemnation released by this suggestion was headed by a leading article in *The Lancet* the following week.[30] The editor questioned the technical feasibility of the operation, whether the valve cusps would stay divided if operation was performed, and whether the symptoms would be relieved even if the operation could be performed. They expressed the belief that this suggestion was so potentially dangerous that "suggestion of surgical operation for the relief of mitral stenosis casts a grave responsibility upon Sir Lauder Brunton." There followed a letter from W. Arbuthnot Lane,[31] stating that he had suggested this same procedure to Dr. Lauriston Shaw several years earlier. In this letter he expressed his belief in the feasibility of such a procedure. Dr. Shaw however, in a later letter, repudiated this belief and stated that he was glad he had never been foolish enough to attempt such an operation.[32] Another castigator arose in the person of Theodore Fisher, who agreed wholeheartedly with the objections raised by *The Lancet* editors. In addition, he cited the factor of rheumatic myocardial insufficiency, then believed to be the most important factor in causing symptoms of mitral stenosis.

It can be seen readily that the suggestion of Sir Lauder Brunton was not received enthusiastically by the medical profession. However, the fact that it created the furore it did should have been encouraging. At least he appeared to have made an impression of some sort, whereas D. W. Samways,[34] who had made the same suggestion in *The Lancet* in 1898, had been completely ignored.

From this rather unimpressive beginning, one may proceed to a consideration of the more significant experimental work related to mitral valve surgery. One of the earliest investigators in this field was Harvey Cushing,[35] who needs no introduction here. His work in this field was restricted to some rather unsuccessful attempts to create mitral stenosis in the dog. Some time later Bernheim[36] reported completion of this work from the same laboratory. He noted that although the production of mitral stenosis in dogs was difficult, its surgical relief was relatively simple. He recognized that the experimental conditions did not approach those found in humans but believed the operation to be possible in humans despite this.

In 1913, Jeger[37] suggested the possible alleviation of symptoms of mitral stenosis by a shunt from the pulmonary vein to the left ventricle, bypassing the stenotic valve. Nothing further was heard from him regarding this, apparently because of World War I.

The war created a similar hiatus in the records of all researchers in this field. The next significant contribution did not appear until 1922. Allen and Graham[38] then published their initial work on this problem.

They described the cardioscope which they had developed for visualization of the interior of the heart. They had attempted its insertion through the ventricular wall, the atrial wall, and the left atrial appendage. They decided the latter was the most advantageous point of entry. Thirty dogs were operated on by this method, the valves being resected with a small knife attached to the cardioscope, and the procedure was tolerated well.

Allen [39] presented further experimental work in 1924, describing a method of inducing mitral stenosis by laying a loop ligature about the chordae tendineae of the left ventricle and tightening it gradually. At this time, all experimenters believed that any procedure designed to relieve mitral stenosis must necessarily result in mitral insufficiency. Allen reaffirmed this belief but stated that he still believed mitral insufficiency to be less damaging than mitral stenosis because the pulmonary hypertension caused by it was intermittent rather than constant, as is the case with the latter.

At this time several groups apparently felt they were ready to attempt the surgical procedure on human beings. Doyen, cited by Cutler,[40] had attempted to separate a stenotic pulmonic valve in 1913, but this patient died after it had been determined that he also was suffering from an interventricular septal defect. In 1914, Tuffier, cited by Cutler,[40] performed a successful finger dilatation of a stenotic aortic valve. Cutler, Levine, and Beck [41] attempted three mitral valvotomies in 1923 and 1924, using a tenotome, and then five more from 1924 to 1928, using a cardiovalvulotome which they had developed. This latter procedure was really a partial valvulectomy, as the valvulotome was designed in such a fashion as to remove a portion of the valve leaflet. In 1925, Souttar [42] performed a digital dilatation of a stenotic mitral valve with improvement of the patient. No further mention was made of his operation, but, of all those done in these early days, his was the one which most nearly approached the procedure as it is performed today. Pribram [43] performed another partial valvulectomy in 1925, using a cardiovalvulotome similar to that of Cutler and Levine, and with the same disastrous result.

Little else was heard concerning such procedures in humans until 1929. At that time Cutler and Beck [40] collected and reported all cases of valvular surgery done to date. There were 12 patients, only 2 of whom were living, the remainder having died a few hours to a few days after surgery. They closed their paper with these discouraged and discouraging words: "It may seem that the information obtained from the 12 cases of chronic valvular disease in which operation was performed is so meager that further attempts are not justified. However, . . . we feel that further attempts are necessary. . . . Unfortunately, our own attempts along this line have been as unsuccessful as the attempts of other and more experienced investigators."

It would appear that no one in the field of surgery at that time felt capable of "picking up the torch" which these men "threw from failing hands" with those last words. Cardiac valvular surgery was apparently forgotten for almost 20 years. One can only speculate as to the reasons for this. Such speculations must surely lead into many ramifications of the philosophy of medicine, upon which I am not qualified to comment. It will, therefore, be left to the reader before beginning a consideration of the "modern" phase of mitral valve surgery.

One of the most distressing symptoms encountered in patients with mitral stenosis is pulmonary edema. Sweet and Bland [44,45] noted that patients with Lutembacher's syndrome did not suffer from this symptom. Upon consideration of the pathologic physiology of the two conditions, they believed that the difference in symptomatology was due to the presence of an interatrial septal defect which served as a "safety valve," allowing blood to go from right to left when acute pulmonary hypertension

developed. With this background, they attempted to simulate the conditions of Lutembacher's syndrome by performing a pulmonary vein to azygos vein anastomosis, thus creating a right-to-left shunt. The first patient in whom this was performed was reported on in 1948,[45] and this was subsequently done in five other patients by these men. Three of these six patients improved temporarily but again worsened when this anastomosis was occluded by thrombus. Harken, Ellis, and Norman[46] attempted to attack this problem from another angle. They created interatrial septal defects in two patients who had mitral stenosis and in whom attacks of acute pulmonary edema were a prominent symptom. These patients also were benefited for a short while, but upon return of their full-blown symptoms, it was recognized that this procedure did not offer the relief it had been hoped it would.

It is universally recognized that the attacks of pulmonary edema suffered by some patients with mitral stenosis are associated with paroxysms of rapid heart action. Harken and Ellis[46,47] proposed that patients in this group whose rapid heart action was not controllable by medical means could perhaps be benefited by cardiac denervation. They presented a single patient on whom this procedure was performed in 1948. The patient was benefited somewhat, but a more definitive procedure came on the scene at this time—mitral commissurotomy.

Smithy,[48] himself a victim of mitral stenosis, undertook surgical treatment of this condition. Despite the unfortunate experiences of earlier workers, his procedure was modeled after that of Cutler and Beck. He constructed a cardiovalvulotome which could be inserted through the heart wall, passed through the mitral orifice, and then manipulated so that a small portion of one of the valve leaflets was resected. Eight operations of this type were performed on seven patients, with two deaths, one unchanged, and four improved. Unfortunately Dr. Smithy died before this work was published, and no further experiences with his procedure have been reported.

Extensive experimental work with dogs done by Bailey[49] led him to conclude that surgical treatment of mitral stenosis was possible with the following reservations: 1. The approach through the left atrial appendage is most satisfactory. 2. The production of mitral regurgitation is poorly tolerated. 3. The valve must be palpated before a cutting instrument is placed in the commissures. 4. The heart tolerates an exploring or manipulating finger in the atrium well. Having arrived at these conclusions, he first attempted to use this procedure on a patient in 1945. The patient died at surgery because of a torn left atrium with hemorrhage. The second attempt was made in June, 1946. In this patient the valvulotome could not be pushed through the mitral orifice and the commissures were separated by finger fracture. The patient died 30 hours later however, and at autopsy the torn commissural edges were found to be reagglutinated. After two other attempts with similarly discouraging results, Bailey's first successful valvulotomy was completed in June, 1948. Since that time he and his group have performed over 1000 of these procedures, with steadily decreasing mortality and increasing good results.[50] In this series of operated-on cases, the operative mortality was 7.9%; the late mortality, 5.6%, and improvement in symptoms was noted in 89.9% of the patients.

Shortly after this, Harken and Ellis,[47] in Boston, and Sir Russell Brock,[51] in Great Britain, working independently, performed similarly successful procedures. The differences in technique were negligible in these early stages, and, with the passage of time, each operator has used the better features of the techniques of the other. Thus, although Baker and Brock[51] call the procedure mitral valvotomy, Harken and Ellis[46,47] call it mitral valvuloplasty, and others[53,55,56] call it mitral commissurotomy, there is little or no difference in its performance in the operating room. Harken

and Ellis have now operated on 1000 patients, 500 of whom have been reported in the literature.[52] Brock and his group have reported 450 operated-on cases also.[9] The statistics for mortality and improvement differ little from one series to another. It is estimated that over 3000 of these procedures have been performed throughout the world. Originally considered a hazardous procedure which should be undertaken only in a teaching center, it is now performed with impunity in many community hospitals.[53-57]

Future of Surgical Treatment

A survey of the statistics cited above leaves little doubt that a technically good operation has been achieved. The medical profession is now faced with another problem, that of evaluating the efficacy of the procedure. The difficulties attending such an evaluation were alluded to in the earlier section on the natural history of mitral stenosis.

Soloff and Zatuchni[58] comment on the difficulty of this evaluation. They emphasize that the course of mitral stenosis is extremely variable, with spontaneous and medically induced remissions sometimes lasting for years. It is pointed out that many patients will have subjective improvement after thoracotomy alone, without the heart being opened. In consideration of some of the results of surgery reported, these authors stress that reports should be presented in such a manner and for a sufficiently long follow-up period that it can be demonstrated that medical and naturally occurring factors could not have been responsible for the changes noted. An accurate evaluation of this sort is necessary because this operation carries a 6% mortality while the annual mortality of conservatively treated mitral stenosis is 1%.

In a later work these authors[59] reemphasize the points made above. In addition they point out a number of factors which cannot be foreseen before surgery. These are (1) failure of function of heavily calcified leaflets even though they are freed at the commissures, (2) a subvalvular stenosis which is not relieved by surgery, (3) reactivation of rheumatic fever, (4) surgically induced or previously undiagnosed mitral insufficiency, and (5) failure to increase atrioventricular flow because of permanent atrial wall or pulmonary vascular changes.

Another aspect of this same difficulty is mentioned in a report by Glover[60] of patients followed three and one-half to six and one-half years after surgery. Of these 50 patients, 82% are still living. An objective estimate of the number improved made by surgeon and cardiologist was 73%, while the patients and family physicians felt that 88% of them were improved.

A similar series is reported by Baker, Brock, and Campbell,[61] composed of 45 patients followed four to seven years after surgery. These authors feel that postoperative improvement is best correlated with the size of the valve opening achieved at surgery. They are most optimistic about the prognosis of patients whom they know were afforded an adequate opening at surgery. There is even greater optimism if there has been an appreciable change toward normal of the physical or accessory clinical findings. They are less optimistic if there was a less complete valvotomy even if the physical signs are improved. If the valvotomy was inadequate and the physical examination shows no change or a worsening, even in the face of subjective improvement, the prognosis is guarded.

Pampush and Bruce[62] and Bergy and Bruce[63] have done studies of patients with mitral stenosis, treated medically and surgically. They used a standard exercise tolerance test as one factor in a formula for determination of the "physical fitness index." Using this test they found that only 55% of patients after commissurotomy had a positive correlation between subjective response and improved exercise tolerance. They also showed that unoperated-on patients, with intensive medical treatment for a year, could achieve a similar improvement.

Another problem, that of recidivism in operated-on cases, is considered by Cordice and Dubost.[64] Although many cases of so-called restenosis have been reported, only 11 of these are considered by these authors to be well-documented cases. The difficulty more frequently lies in an inadequate commissurotomy rather than true restenosis. This problem therefore is of little concern at present, although it may become more important with the passage of time.

It becomes obvious, therefore, that there are two needs for evaluation of the efficacy of mitral commissurotomy: (1) a method of direct measurement of changes in mitral valve hemodynamics which is less hazardous than open cardiotomy and (2) a sufficiently long follow-up period to determine accurately whether the operation really modifies the pattern of the disease. The former is now available to us in the form of left-heart catheterization. The latter must wait for the passage of time.

Conclusion

This survey shows then, that the present surgical therapy for mitral stenosis has had a long, rather difficult, evolution. This began with the recognition of the characteristic signs and symptoms and their association with certain structural abnormalities by Vieussens. Following this there were many years of study which elucidated the pathologic physiology and natural history of the disease. Beginning with the proposals of Samways, in 1898, and Brunton, in 1902, surgical correction began to be considered as practicable. Many more years of experimental and clinical study were necessary before Bailey performed the first successful mitral valvulotomy, in 1948. Since that time surgical intervention has become widely accepted, and now, even though not perfect, it is considered the treatment of choice in certain selected cases of pure mitral stenosis with progressive incapacitating symptoms. A brief glance into the future shows that there are questions yet to be answered about this therapy but that observations over a period of years will be necessary before these questions can be answered completely.

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Contributions of Basic Science to Modern Medicine

Some Interrelations Between Sleep and Disease

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There are a number of physiological differences between the sleeping and the waking state. The implications of these differences for the patient with disease have not been widely explored.

It is the purpose of this review to indicate by means of specific examples how some of the physiological changes associated with sleep may affect the pathologic physiology of some diseases. No attempt will be made to discuss every area in which it is known that the physiologic changes of sleep and disease overlap. Rather, this review will set forth some examples of mechanisms by which sleep may modify pathologic physiology. For this purpose, the following topics will be discussed:

1. The basic nature of sleep
2. Sleep and the control of ventilation
3. Sleep and cardiovascular function
4. Diurnal variation of adrenal function and its clinical significance
5. Sleep and red cell metabolism in paroxysmal nocturnal hemoglobinuria
6. Sleep and the host-parasite relation in filariasis
7. Sleep and blood sugar regulation

1. The Basic Nature of Sleep

The basic nature of sleep is not known. Theories to explain its genesis date back to at least the sixth century B. C.[1] A partial list of such theories is as follows:

I. Chemical theories
  A. Non gases
    1. Hypnotoxin
    2. Lactic acid
    3. Cholesterol
    4. Urotoxins
    5. Hypercalcemia
    6. Alcohol and ureides
    7. Fatigue toxins
    8. Bromide-containing hormone of the anterior pituitary
    9. Wakefulness-producing hormone
    10. Magnesium
    11. Thyroid hormone lack
  B. Blood gases
    1. Hypoxia
    2. Hypercapnia
II. Hemodynamic theories
  A. Cerebral anemia
  B. Cerebral plethora
III. Neural theories
  A. Sleep neurones
  B. Sleep center in hypothalamus
  C. Sleep center in thalamus
  D. Sleep center(s) in cerebral cortex
  E. Generalized cortical inhibition
  F. Dendritic withdrawal theory
  G. Vagotonia
  H. Sympathetic-parasympathetic imbalance
IV. Psychological theories
  A. Sleep as an instinct
  B. Sleep as a function of vital principle

All such theories have either been based on inadequate experimental evidence or have provided inconclusive or inconsistent explanations for the sleeping state.

One fundamental reason for the lack of success in discovering an "etiology" of sleep is that the wrong question has been asked. Most workers in this field have asked, "What causes sleep?" In reality, the question should be asked, "What causes the waking state?"

Specifically, it has been shown that a number of active neural mechanisms are necessary for the waking state to be main-

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tained. These mechanisms include the reticular activating system described by Magoun,[2] a hypothalamic waking center,[3] certain cortical waking centers,[4] afferent impulses arising from the various modalities of sensation,[1] and undoubtedly other neural mechanisms which have yet not been described.

In terms of this concept, sleep is the normal or usual state of the organism. The "sleeping" centers of the older literature now properly become "waking" centers, and waking only occurs as a result of the operation of these centers.

Such a concept of sleep is useful for several reasons. It is consistent with most modern experimental evidence on brain mechanisms and consciousness.[5] It is consistent with modern views on ontogeny and phylogeny.[1] It permits one to view sleep not as an isolated or static state. The transition from waking to sleeping becomes analogous not to switching a radio off but to the volume control of a radio set. Gradations of this transition may be viewed as greater or less functioning of the neural mechanisms responsible for the waking state. Sleep is thus regarded not as a single undifferentiated state—but, like the waking state, a time of great and varying physiological and metabolic activity.

2. Sleep and the Control of Ventilation

The depression of specific neurogenic controls during sleep is one mechanism by which sleep may modify disease. This may be illustrated by the changes in the control of ventilation during the sleeping state.

It has been known for a number of years that alveolar CO_2 tension increases during sleep in normal subjects.[6,7] Recent work has indicated that this rise in alveolar CO_2 tension is caused by a depression of respiratory center sensitivity to CO_2.[8] This depression of respiratory center sensitivity occurs rapidly after the onset of sleep and is rapidly reversed by the waking state. It appears that the sensitivity of the respiratory center to CO_2 is dependent on, among other factors, afferent impulses coming to it from numerous areas in the nervous system. During the waking state, the number of afferent impulses is relatively large, producing a brisk alveolar ventilation and resulting in a normal waking alveolar CO_2 tension. During sleep the number of impulses is decreased and the responsiveness of the respiratory center consequently decreases. The result is a decreased level of alveolar ventilation and a rise in alveolar CO_2 tension until a new steady state is achieved.

During the sleeping state, the fall in alveolar ventilation averages approximately 1.5 liters per minute, the rise in alveolar CO_2 tension averages approximately 5 mm. Hg, and pH falls approximately 0.03 pH units. Further, as a result of respiratory center depression, there is a considerable incidence of periodic breathing in normal sleeping subjects.

These changes are all quantitatively important but are of such an order of magnitude that the normal subject does not suffer from clinically significant hypoxia or hypercapnia during sleep.

The situation is different in the subject with chronic pulmonary disease and chronic hypercapnia. It has been shown that such subjects show a depression of respiratory center sensitivity to CO_2 while *awake*.[9] Under these circumstances, it is to be expected that the patient with chronic pulmonary disease should show more profound elevations of CO_2 and a more profound depression of respiratory center sensitivity during *sleep* than do normals.

This is indeed the case. In a study of seven subjects with emphysema and chronic hypercapnia, it has been shown that the average increase in alveolar CO_2 tension during sleep was approximately 10 mm. Hg—2.5 times the average increase in normals.[10] Four of the seven patients studied showed florid Cheyne-Stokes breathing while asleep.

The magnitude of the decrease in alveolar ventilation sufficient to produce the normal 4 mm. rise in CO_2 tension is insufficient to produce significant arterial unsaturation. Since the saturation value of normal arterial

blood falls on the flat part of the oxyhemoglobin dissociation curve, a relatively large decrease in alveolar oxygen tension is necessary to produce a significant fall in arterial oxygen saturation.

The magnitude of the fall of alveolar ventilation sufficient to produce a 10 mm. increase in alveolar CO_2 tension is sufficient by itself to produce arterial unsaturation. In addition, patients with hypercapnia are invariably unsaturated awake. Their saturation values fall on the steep part of the oxyhemoglobin dissociation curve, and a relatively small decrease in alveolar oxygen tension will produce a relatively large decrease in arterial oxygen saturation. Under these circumstances, it is likely that patients with emphysema are significantly more unsaturated asleep than awake.

Therefore, the subject who is hypoxic and hypercapneic awake will have these defects magnified by sleep. This finding correlates well with the clinical observation that the patient with severe emphysema has his most difficult time soon after awaking.

It can thus be seen that a normal physiological change associated with sleep may have deleterious consequences for the patient with disease.

3. Sleep and Cardiovascular Function

The assumption of the horizontal position for a significant period of time is another mechanism by which sleep may modify disease. This may be illustrated by changes which occur in hemodynamics during sleep.

It has been shown that there is an increase in plasma volume in normal subjects during sleep. This increase is produced by the entrance of extracellular fluid into the intravascular compartment. At the end of eight hours of sleep, this increase may amount to 15% of the waking plasma volume.[1] It has also been shown [11] that this increase in plasma volume could be duplicated by merely assuming the horizontal position for 20-30 minutes without actually going to sleep.

This increase in plasma volume is explained by alterations in capillary-tissue hemodynamics in the upright versus the reclining position. In the upright position, there is an increase in capillary filtration pressure, with a loss of protein-poor fluid to the tissue spaces. In the horizontal position, there is a decrease in capillary filtration pressure and a return of fluid to the vascular compartment with an increase in plasma volume.

In addition to the over-all increase in plasma volume during recumbency, there is pointed out that an average of approximately a redistribution of blood. Sjöstrand has 600 ml. of blood was shifted from the lower extremities to the rest of the body after five standing subjects assumed the reclining position. Seventy-eight per cent of this blood was taken up in the thorax, three-quarters of which was accommodated in the lungs. Thus, blood is shifted from the lower extremities to the pulmonary circulation.[12] In the normal subject, the increased plasma volume and relative pulmonary plethora are tolerated without difficulty.

The situation is different in the patient with left ventricular disease. In such patients, factors which increase venous return or pulmonary blood volume tend to increase pulmonary congestion and produce pulmonary edema.

Paroxysmal pulmonary edema occurs most commonly at night and after some period of recumbency. This association between sleep and pulmonary edema is a classical feature of left ventricular failure and has been given the descriptive name of "paroxysmal nocturnal dyspnea." These episodes can often be aborted by the patient sitting upright or by walking or can be prevented by having the patient sleep with the head of his bed elevated.

Although other factors may also play a role in the pathogenesis of paroxysmal nocturnal dyspnea, it is clear that a major factor is the change in hemodynamics associated with the recumbent position. Recumbency thus represents a second mechanism through which the physiological changes of sleep and disease overlap.

4. Diurnal Variation of Adrenal Function and Its Clinical Significance

The occurrence of diurnal cycles is another mechanism by which sleep may modify disease. As an introduction to this topic, it is useful to discuss the general nature of biological rhythms. Cole [13] has recently presented a brilliant critique of the concept of biological cycles. The interested reader is referred to the original article for the details of this analysis. Cole points out that there are two fundamental types of cycles. On the one hand, organisms may exhibit exogenous rhythms and have their periods of activity related to changes of various physical phenomena, like light intensity, humidity, or phase of the moon. On the other hand, organisms may have endogenous rhythms that are present in the apparent absence of external stimuli. In theory, it is not difficult to conceive of mechanisms for generating rhythms in the absence of external stimuli. For example, a hormone might accumulate until it reaches a threshold value that initiates the activity in question and simultaneously begins to exhaust the store of hormone.

However, it is difficult to shield the organisms from all of the external stimuli impinging upon it. Innate rhythms and exogenous rhythms of different periods may be intermingled and lend a further appearance of complexity to raw data. In practice, the approach that is used is to amass raw data and subject it to some form of statistical analysis. This approach is hazardous because time series sometimes yield what has been called by Yule [14] nonsense correlations, i. e., causal connections between obviously unrelated events. For this reason, data purporting to prove a true biological cycle must be most critically evaluated.

In any case, there appears to be good evidence that there is a diurnal variation in the plasma levels and urinary excretion of adrenocortical hormones.[15-17] It appears that under basal conditions the adrenal secretes approximately 70% of the daily secretion of hydrocortisone from 12 midnight to 9 a. m. Thus it appears that the major portion of adrenal cortical activity occurs during sleep and in the early morning hours. This adrenal cycle is probably independent of sleep habits, since in night workers the fundamental cycle does not change.

This normal cycle may have important implications for the patient with disease. It has been pointed out that when inhibition [18] of adrenal cortical activity is desirable, as in the treatment of the adrenogenital syndrome a dose of hydrocortisone will prove nearly twice as effective when given at night as when administered in the morning. When adrenal cortical inhibition is to be prevented, as in the therapy of allergic disorders, the time of drug administration may be important in terms of the total corticoid supply achieved. Administration of a single small dose of steroid early in the morning will supress spontaneous adrenal secretory activity only during the hours of relative inactivity and thus become nearly additive to the 24-hour output from the adrenal glands. On the other hand, the same dose given every six hours in divided doses will suppress endogenous adrenal secretory activity during the active period of secretion, so that little will be gained by giving the drug in this manner.

The most direct clinical implication of the diurnal cycle of adrenal cortical secretory activity relates to patients with rheumatoid arthritis. Studies of urinary 17-hydroxycorticosteroid excretion [19] and plasma corticoid levels [20] indicate no marked total decrease in adrenal steroid excretion. However, in some patients there appears to be a modification of the diurnal cycle, so that the early morning peak of adrenal activity is lost. This loss of early morning peak has been correlated [20] with the morning stiffness frequently shown by patients with rheumatoid arthritis. Thus, modification of a diurnal cycle represents another mechanism by which sleep may modify disease.

5. Sleep and Red Cell Metabolism in Paroxysmal Nocturnal Hemoglobinuria

The presence of metabolic differences between the waking and sleeping state is another mechanism by which sleep may modify disease. This may be illustrated by the changes in red cell metabolism in patients with paroxysmal nocturnal hemoglobinuria (P. N. H.).

Paroxysmal nocturnal hemoglobinuria is a disease characterized by signs of hemolytic anemia and marked by episodes of hemoglobinuria. A distinctive feature of the syndrome is that frequently the hemoglobin either is present in the urine only during sleep or else increases greatly during the period of sleep as compared with the waking period.

The primary fault appears to be in the erythrocyte. There is no evidence of inherent abnormality in the serum, although factors present in normal serum are necessary for hemolysis to occur.[21]

The relationship of hemolysis to sleep is definite. Most patients show higher plasma hemoglobin levels during sleep than during the waking state. If the pattern of sleep is reversed so that the subject sleeps during the day and is awake at night, maximal hemolysis now takes place during the day.[22]

The exact nature of the metabolic changes occurring during sleep and giving rise to increased hemolysis in the disorder is unknown.

It has been shown that increased acidity in vitro produces a marked increase in hemolysis of P. N. H. erythrocytes.[23] This is indeed the basis of the Ham test for this disorder. On this basis it has been suggested that the increase in alveolar CO_2 tension and fall in pH during sleep are responsible for the increased hemolysis. Recent work has shown that this is not the case.[24] Plasma hemoglobin levels during sleep do not correlate with the changes in CO_2 tension and pH. Moreover, the magnitude of the increase in alveolar CO_2 tension and fall in pH during sleep is not sufficient to provoke increased hemolysis in patients with P. N. H. When such patients are exposed to inhalation of 6% CO_2, producing increases in alveolar CO_2 tension and decreases in pH much greater than occur during sleep, no significant increase in plasma hemoglobin can be demonstrated.

Although the exact nature of the metabolic changes producing increased hemolysis during sleep is not known, the nocturnal hemolysis of P. N. H. is clearly an example of how metabolic changes during sleep may modify disease.

6. Sleep and the Host-Parasite Relationship in Filariasis

Another mechanism for the alteration of disease during sleep is a change in the host-parasite relationship occurring during this state. This mechanism may be illustrated by a consideration of filariasis.

Filarial periodicity was first described by Manson, cited by Hinman,[25] in 1883. He noted that Wuchereria bancrofti could most easily be found in the blood only between 12 midnight and 2 a. m. During the day the microfilariae returned to the viscera and were therefore inaccessible. Shortly thereafter Mackenzie, cited by Hinman,[25] was able to invert the cycle by reversing the period of sleep and activity of the host. This observation led to a long series of experiments endeavoring to elicit the mechanism of this phenomenon. Two main theories have emerged. One theory holds that there is cyclical parturition of the female filarial worms, with rapid destruction of the microfilaria. The other theory holds that there is continuous production of embryos with their temporary removal from the peripheral circulation during the daytime through some unknown factor. The bulk of evidence would seem to favor the latter theory.

Body temperature,[26] metabolic changes in the blood of the host,[27] and a chemotactic substance in the saliva of insects producing a stimulus for cyclic parturition[28] have all been advanced as possible mechanisms for filarial periodicity. Although its mechanism is unsettled, the occurrence of filarial perio-

dicity is a clear example of the modification of host-parasite relationship by sleep.

7. Sleep and Blood-Sugar Regulation

The final mechanism to be discussed is not a physiological mechanism. It is based on the fact that observations of patients are generally limited to waking hours. To the physician, the patient lives on a 16-hour-a-day basis. In reality, man is a 24-hour-a-day organism. This mechanism may be illustrated by the changes in blood sugar in diabetics during sleep.

Determinations of blood-sugar levels during sleep in normal subjects reveal a remarkable homeostatic mechanism.[29] The hourly variation in blood-sugar concentrations during sleep is extremely small. Moreover, if carbohydrates are administered to sleeping normal subjects, there is a rapid return to basal levels of blood sugar.

It appears that blood-sugar regulation has nothing to do, per se, with sleep. Studies on reclining fasted subjects showed the same constancy of blood sugar. This constancy is apparently based on an effective regulating mechanism operating at a time when demands on it are minimal, i. e., at a time when it does not have to deal with additional exogenous carbohydrate furnished by eating or increased glucose utilization produced by exercise.

The situation is quite different in the patient with diabetes mellitus. Such patients are insulin-deficient, and they also lack an effective mechanism for blood-sugar regulation. It is not surprising that one finds fairly wide variations in blood-sugar concentration during sleep.

These wide variations are present first of all in the untreated diabetic. The hour-to-hour constancy of blood sugar in the normal is replaced by marked variations during the night. Factors in this variation include the time and nature of the previous meal, the severity of diabetes, the state of liver glycogen, and the sensitivity of the sugar-regulating mechanism to changes in sympathetic nervous system activity.

Wide variations are also present in insulin-treated diabetics. In such patients the physician attempts to substitute insulin in type and amount that will keep the patient's blood sugar at physiological levels. However, the physician substitutes a biochemical substance and not a physiological mechanism. Insulin will be released from the site of injection at a rate not determined by changes in blood sugar but determined by the type and amount of insulin. It is not surprising that the physician's *guess* as to what constitutes adequate insulin dosage may be quite inaccurate. Since the blood-sugar concentrations of patients are not usually determined during sleep, the discrepancies between insulin dosage and insulin need might be expected to be great during this time.

Almost any pattern of blood-sugar concentration change may be found during sleep in insulin-treated diabetics. Profound hypoglycemia, progressive hyperglycemia, and periods of hyperglycemia and normoglycemia are examples of the patterns found during sleep in treated diabetics. It is obvious that the eight hours of sleep which are usually ignored in the diabetic are important in the over-all regulation of his disease. Thus, the inaccessibility of the sleeping patient becomes a mechanism which modifies the therapy of his disease.

Summary

The sleeping patient is still a patient. His disease not only goes on while he sleeps, but indeed may progress in an entirely different fashion from its progression during the waking state. The interrelations between sleep and the pathologic physiology of disease constitute a fruitful field for a more complete understanding of many diseases.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

1. **The Art of Teaching.** By Gilbert Highet. Price, $1.25. Pp. 259. Vintage Books, Inc. Reprinted by arrangement with Alfred A. Knopf, Inc., 501 Madison Ave., New York 22, 1957.

2. **The Arts of Living.** Edited by Gilbert Highet. Price, $3.00. Pp. 190. Simon & Schuster, 630 Fifth Ave., New York 20, 1954.

3. **Poets in a Landscape.** By Gilbert Highet. Price, $6.95. Pp. 267, with illustrations. Alfred A. Knopf, Inc., 501 Madison Ave., New York 22, 1957.

This review of three books written or edited by Gilbert Highet has as its purpose calling their author to the attention of physicians who read this note. Too many of us are unaware of writers outside of our own narrow zone of medical or scientific specialty. One of my purposes in writing book reviews is to call attention to writers whom I have found stimulating, interesting, and invigorating.

Every doctor must have a concern for teaching and education, whether he still has a close or remote connection with a medical school or not. This is because every physician worthy of the name must continue to be a student. He must be his own teacher, with some help from others if he can get it. The more he knows about learning and teaching, the more likely he is to keep himself fit for medical practice, directing his own perennial and perpetual refresher course as time goes along. But in a still higher sense, as Highet points out in this delightful book, "The Art of Teaching," the patient must be taught too. Here the effectiveness of the doctor as teacher gets its sternest test. So much of what we do in medicine today is not the miraculous intervention to achieve by surgical tour de force or miracle drugs a cure for a particular state or disease. Rather it consists of providing the patient with enough information and encouragement to enable him to become the major effecter of his own cure. Today treatment is not a single given act, an operation, or a prescription, but a long, often lifelong, program. This is true particularly for many conditions now common in the practice of internal medicine, such as the management of the diabetic patient, control of the cardiac patient, or the perpetual dieting of the obese. Unless we learn to teach patients, our practice will be ineffectual. We will have failed in that one essential of the good physician, namely, caring for the patient.

Actually "The Art of Teaching" is directed toward persons who fill the more formal role of teacher. Thus it has special relevance for anyone in academic medicine. This book takes the role of teaching far beyond its ordinary confines and demonstrates how important it is in everything we do, think, or say. When we consider the two ways in which mankind and various societies are enabled to survive, the genetic mechanisms of physical inheritance, and the perpetuation of culture by the processes of education, the importance of teaching comes into sharp focus. We do well to think about it and work on it in order that we may become excellent teachers.

It is refreshing and comforting to review some of the frequently neglected or overlooked points which Highet emphasizes. For instance, we may forget the natural resistance to a teacher by the pupil, human inertia, and the monolithic phenomenon of widespread ignorance.

The first essential of good teaching is that the teacher know the subject, and continue to keep it fresh by continuing to learn it himself. Highet recognizes that all good teachers may dislike some part of their subject. This they compensate for by hard study or by emphasis on those elements in which they excel. The second essential is that all good teachers must like to teach and must have an interest in, indeed must love, what they are teaching. The third essential of good teaching is that good teachers must like their pupils. The often forgotten corollary is that one must recognize the pleasure and necessity of escaping completely from pupils from time to time, whether the refuge be a garden oasis, a trip, or a nook in the library.

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Highet reminds us that few people continue to grow after that curious intellectual terminus in the thirties, the mental climacteric most of us deny and few relish discussing. Too many settle down and stagnate, or at the most continue to coast on momentum from earlier work.

In emphasizing the usefulness of humor, Highet says that scientific subjects do not admit of humorous treatment. Here I disagree with him, for I sometimes see ridiculous aspects in almost anything, even if it be merely the pomposity of the self-appointed elite in a solemn field.

What are the methods and means of a good teacher? First of all, *memory*. We must have stashed away, written down on the tablets of our mind, a vast volume of images, facts, and data in a system which puts to shame even the most elaborate monster of an electronic "brain." Memory depends not only on natural gifts, but on cultivating attention and gaining skill in making all kinds of associations. Second only to memory comes will power, or if you prefer, *determination*. One must be firm and efficient, one must demand of pupils concentration to which their mind has naturally or has formed a natural antipathy, a repugnance closely akin to the resistance to work which seems to be second nature to most of us. Concentration can be learned and it must be learned early. The third quality of a good teacher is *kindness*, which must be genuine, and not forced. These characteristics which Highet sets forth as the essence of the good teacher are actually requirements of the good person. A good practicing physician, a specialist, a general practitioner, or a scientist immersed in the minutiae of the laboratory and the excitement of his own activities, all, need them equally.

As for methods, Highet emphasizes preparation. He sums up his advice in the admonition, "Always read the original sources," a general statement of the classic admonition, "Always check your references." After preparation, one has to be able to do what is called, in the crude lingo of our day, communicate. In short, a teacher must teach. He must convey his own thoughts, ideas, and personality to his pupils who are to be taught. This can be done in an infinite number of ways. Basically it consists of the ability to transfer ideas, to make them graphic, to make them vivid, and to make them interesting. Good teaching confers on the student the enthusiasm of the teacher. If the teacher is great, this provokes an epidemic of learning, which may spread almost infinitely and in unmeasured ways.

The processes of teaching are lecturing, the tutorial system, and what essentially is an exercise in doing—the standard method of teaching languages, literature, history, and the descriptive sciences such as biology, anatomy, and botany. This is the laboratory exercise, what the unimaginative are pleased to call a "workshop." It is the use of patients at the bedside to demonstrate and discuss, the laboratory activity of trying and doing with one's hands, the actual dissecting and drawing. To this exercise textbooks are never more than a subsidiary aid.

Two further sections of Highet's book contain a fascinating discourse on great teachers and their pupils, and teaching in everyday life. They are just as charming and certainly as useful for the doctor in practice as they are for the teacher, physician, or scientist in academic medicine.

One finds reflected in these pages the warmth of a scholar, the joy of a teacher, and the enthusiastic delight which bubbles forth in Highet's books and makes his writings not only pleasant to read but a stimulus to better performance. If his wise words could be employed as they are meant by more doctors it would be to the lasting benefit of medicine.

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It seems unlikely that many people who are reading this review will have spent much time reading *Vogue* magazine. If they have not done this during the past decade or so, they will have missed a remarkable series of essays on "The Arts of Living," brought together in a fine little book by Highet. He describes his own interesting experiences in gathering a most unlikely but delightful group of essayists whose efforts Highet has divided into three sections, entitled "Arts of the Mind," "Living with Oneself," and "Living with Others." Among the contributors to this collection are poets, editors, divines, college administrators, teachers, critics, novelists, lecturers, reporters, immigrants, native Americans, foreigners, and several who defy classification or properly fall into several classes. The omission of physicians indicates how little worthy they are considered to contribute to so elegant and charming a collection. In the section on "Arts of the Mind" are essays on The Art of Concentration; of Skepticism; of Curiosity; of Discovery; and of Keeping the Mind Refueled. In the section about Living with Oneself, we find The Art of Accepting Oneself, of Being Conservative; of Living in the Present; of Beginning Where You Are; of Discontent; of Courage; of Balancing Time; of Adventure; of Using What You Have. This book really has a star cast, including Ernest

Dimnet, Rebecca West, Charles Morgan, Oliver LaFarge, Elizabeth Bowen, Russell Lynes, Malcolm Muggeridge, and Gilbert Highet himself, just to mention some at random, for the ones I left out are equally perceptive. The imaginative contribution made by Highet was to fetch together this enchanting company of people whose single common denominator was that they wrote for *Vogue* and to give them an opportunity to write on the arts of living. How they embellished this theme is illustrated with wisdom, with perception, and with sufficient grace and style to be used as a model for such things.

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The troublesome technical problems of translation are aggravated in translating the classics into modern languages. These troubles are compounded when we translate poetry, because rhyme, meter, emphasis, tune almost, rhythm, and cadence have different values in different languages. Thus a successful translator must be poet as well as scholar. Few of our generation had a broadly based education in the classics. At least some of those who were exposed were so unhappy in the dry details of grammar that they never got beyond the dust into the rich treasury of language wherein lurked the artists, poets, soldiers, rulers, and people of classical antiquity. Whether one knows Latin and Greek or not, a classical education, valuable for the discipline of learning how to interchange ideas from one set of symbols to another, had its chief virtue in giving a comprehension of how various peoples confronted their problems in times gone by. The problems are forever repeating themselves. Ancient solutions sometimes still work.

This book takes us on a visit to the country of classical Roman greatness as seen today by a most perceptive traveller. Not only does he evoke the magic moods of Italy as a garden spot with his exquisite photographs taken along his pilgrimage to the haunts of his favorite Latin poets; he tells us just enough of each to get the rich savor of the man and his time. The translation of representative portions from each poet are done with the love of a scholar, the perfection of an artist, and the passion of the true pilgrim. The time and temper of each poet are related to Rome as the physical and cultural mother to which each looked. The deeply moving translations have been made as nearly as possible in the exact meter of the original, catching the ryhthm and mood as well as the sense in a scholarly and yet moving tour de force. To match meter and rhythm, the true inwardness of Latin poetry is achieved with skill and grace, although for those not familiar with Latin there is a certain strangeness about some of the verses. Latin poetry ranges from the austere and dignified to the gay and chatty; and a sense of the ironic pervades much classical poetry. The Roman elegy is sometimes even gossipy; the epigrams are conversational, prosaic, and colloquial. Highet has reflected the original poems in tone and mood, and so gives ancient verse the verve and swing of modernity which they had in the pristine times of their presentation to the Roman audience reading them as the journals of their day.

For those whose knowledge of Rome is second- or third-hand, "Poets in a Landscape" comes near being a conducted tour. In sequence Highet gives us a picture of the character and times of Catullus, Vergil, Propertius, Horace, Tibullus, Ovid, Juvenal, and winds up with a comparable character sketch of Rome inself. Everywhere the whole breathes Italy. One gets a clear vision of why Italy has been able to achieve greatness. The lusty and violent but magnificent organizing might of Rome is laid before us; and its magnificent women and the men who tell us of them.

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These three books, each individual, utterly different, will be useful and charming reading for anyone who will put aside the pressing *busyness* of his life and seek wisdom from a master of the arts of teaching, of living, and of that excellence of learning which deserves to be called true scholarship.

WILLIAM B. BEAN, M.D.

The Atomic Age and Our Biological Future. By H. V. Brøndsted; translated by E. M. Huggard. Price, $2.75. Pp. 80. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1957.

In our bewildered age all of us must find supports to cling to—physical, moral, ethical, and spiritual. Above all, we need to face the present and plan for the future, in the light of what we have learned from the past and what we know of the things today, particularly with reference to the biological limitations of living matter, the impersonal ruthlessness of atomic forces, and the not yet very steady efforts of man to develop wisdom to control the knowledge

he has gained by applying on a world-wide scale the frail humane forces which have made tolerable life in families, communities, and small societies. Brøndsted has published a fascinating book which I have read as a layman, and I think it can be read in this fashion by any physician or any scientist. There is a brief, simple, but very lucid exposition of the principles of radiation. It is followed by a discourse on biological principles, on the organization of biological matter, using comprehensible similes to get us oriented in practical matters of the fertilized egg and sexual reproduction. Then the effects of radiation both on the individual person and in terms of the long genetic hopes of man are detailed in clear, forthright and, therefore, ominous intensity and clarity. One gets the sense that we are at the turning point—a crossroads—certainly a point of no return, where any error may bring disaster and where even the most scrupulous care and caution may not be enough, for we may not know enough about the future or in what way living men and all living things may carry the cumulative increments of minor genetic alterations from even small additions to the exposures to naturally occurring radioactivity. Since our vastly complex modern society obviously is at a place where it can never start over, if fatal errors are made, the urgency of the problem is clearly before us. One has the sensation now not necessarily of standing on the edge of the abyss but realizing that one is in the immediate vicinity. Never more starkly or in more horrible intensity have we seen the alternatives to a humane and wise solution to the problem of the atomic age. They are developed in this thoughtful but fearful little book. Even going slowly, one can read it in a couple of hours. Its contents should be known clearly and completely to all thinking persons today. For the all-or-none law will operate. There will be no partial successes and no partial failures. It will be one way or the other, as it was for the hero of Frank Stockton's tale, "The Lady or the Tiger." If man makes the fatal mistake, be it speedy, catastrophic, almost instantaneous destruction, or be it the slow death by damage done to the genetic mechanisms of mankind, building slowly as stalactites and stalagmites in a cave, the result will be equally final. Unless all life is extinguished from the planet, evolution will record the traces of man as another creature who got into a cul-de-sac from which he could not extricate himself; and Nature, not beguiled by fancy, bemused by power politics, or bewildered by wishful thinking, will turn busy hands to try other more hopeful experiments.

WILLIAM B. BEAN, M.D.

Group Processes: Transactions of the Third Conference, Princeton, N. J., 1956. Edited by Bertram Schaffner, M.D. Price, $4.00. Pp. 328. Josiah Macy Jr. Foundation, 16 W. 46th St., New York 36, 1957.

Part of the thesis of the present directors of the Josiah Macy Jr. Foundation is the belief that "the major obstructions to understanding among scientists lie in the resistance of human attitudes to change rather than in difficulties of technical comprehension." On the basis of this belief, the considerable energies of the Josiah Macy Foundation have been directed into the conduct of a series of small conferences of experts working in fields where change in science and medicine is rapid and where interchange of ideas often lags far behind the salient points uncovered by independent and often widely separated workers. I think no one working in any field of science or medicine would deny that the interchange of ideas, the cross-fertilization by close contacts and the stimulus gained from colloquia and symposia, literally, talking together and drinking together, provide perhaps the most stimulating experience there is in the learning-teaching process in medicine and science.

Even with a certain amount of editing, one sometimes wonders about the value of committing to the printed page with its temporary immortality the conversations of even very wise experts, when these conversations are of the most informal kind. So often what has been said in the spirit of gentle irony, quizzically, with an eyebrow raised, or the trace of a wink, comes out sounding pontifical. Sometimes it is not only redundant but hardly worth all the hue and cry. The autobiographical sketches of the various contributors are extremely helpful because these books in effect allow one to be an uninvited interloper at the week-end party of active thinkers who have conspicuous differences in attitudes, qualities, and the capacity to set their thoughts clearly before us. I found by far the most stimulating portion of the book the last chapter, almost a third of the book, which takes up Chinese Communist thought reform. It gave me a very much moderated and modified view of brain washing from that which I had obtained from the daily press and other vague sources. There are interesting points in all the chapters.

Everyone can learn something from each of the various sections of the book, even though at times the conversation wobbles around a little. As I have been musing upon this book and those like it, bound volumes of a weekend's talk, I fell into the mood of Lewis Carroll which accounts for this version of the Jabberwocky:

T'was Mirsky and the Bruner, Hess
Did Schaffner and did Erikson
Fromm-Reichmann all the way to Mead
They Spiegel as they run.
Let us ascend past Fremont-Smith
Birdwhistell there to listen to,
With Liddell Peck and Redl bill
And his Barron call Meerloo.

Oh Bavelas, my Bateson boy
Josiah Macy is the call
No Boguslavsky feigns his joy
To Lifton if you fall
Goffman and Steinbach talk apace
Group process two by two
With Liddell Peck and Redl bill
And the Barron call Meerloo.

WILLIAM B. BEAN, M.D.

Immunopathologie in Klinik und Forschung. By P. Miescher and K. O. Vorlaender. Price, $16.45. Pp. 598, with 119 illustrations. Georg Thieme Verlag, Herdweg 63, (14a), Stuttgart, N (American agent—Grune & Stratton, Inc., 381 4th Ave., New York 16), 1957.

In recent years new information about immunopathology and autoantibodies has been discovered so rapidly that we now have need for a book that records this new knowledge. The book of Miescher and Vorlaender meets this need very well indeed. The principal authors of the book have prevailed upon those workers who have contributed most to the subject in Europe, and each has written about the things with which he is most familiar.

The book starts with a consideration of the experimental background, and there are brief discussions of the general phenomena of immunology and of antibiotics against erythrocytes, leukocytes, and thrombocytes. There is also an extensive review of the experimental production of glomerulonephritis, rheumatic fever, liver disease, and encephalomyelitis. This section is an extremely useful review of the experimental literature and will be read with interest by many laboratory workers.

The second part of the book is concerned with the clinical aspects of diseases resulting from immune responses or from the development of autoantibodies. Each chapter gives a brief general consideration of the subject, followed by the methods for studying each of the diseases and finally a complete consideration of the clinical and laboratory aspects of the various diseases.

The diseases are considered in a systematic fashion. There are chapters on the hemolytic anemias, including the autoimmune hemolytic anemias of the newborn; on the disorders of leukocytes and thrombocytes which have a basis in abnormal immune responses; on the purpuras, and on kidney and liver diseases. There is also a full discussion of the serologic and pathogenetic aspects of rheumatic fever and related syndromes, such as Felty's syndrome, scleroderma, and dermatomyositis. There is a brief chapter on autoimmune reactions in the thyroid, although the book was published just before much of the definitive work on this subject appeared in the journal literature. There is also a chapter on visceral erythematodes and the immunologic aspects of polyneuritis. Finally, there is a consideration of homotransplantation of organs and of sympathetic ophthalmia and some related conditions.

There is not space in this brief review to go into detail about these various chapters; however, many of them make fascinating reading. I was particularly interested in the chapter on the abnormal immune responses in certain liver diseases and in those on the blood

dyscrasias, but anyone who is interested in the abnormal immune responses of the body will find that the book provides much new information and an orderly consideration of the old. As is usual with German publications, the book is a fine example of the book-makers' art.

WILLIAM B. WARTMAN, M.D.

A Follow-Up Study of War Neuroses. By Norman Q. Brill, M.D., Professor of Psychiatry and Superintendent and Medical Director, The Neuropsychiatric Institute, University of California School of Medicine, Los Angeles, and Gilbert W. Beebe, Ph.D., Statistician, Follow-Up Agency, Division of Medical Sciences, National Research Council, Washington, D. C. Part of program of studies of Follow-Up Agency of National Research Council Developed by Committee on Veterans' Medical Problems in Cooperation with Veterans' Administration, the Army, and the Navy. Price, not given. Pp. 393, with 282 illustrations. Superintendent of Documents, Government Printing Office, Washington 25, D. C., 1956.

Little is known of the natural history of the neuroses, very much less than is known of rheumatic heart disease or of multiple sclerosis. A factual study is long overdue. Psychoneurosis accounted for 27% of Army discharges for disability during World War II, and after the war the Veterans' Administration arranged a large cooperative undertaking to follow some of these patients.

This monograph presents the findings. One thousand four hundred seventy-five patients were studied, representing one in two hundred of those admitted to military hospitals in 1944. One in two hundred is a small sampling ratio, but the reliability of the sample is more directly a function of its absolute size than of the ratio employed in selecting it from its parent source. The preservice, service, and postwar histories were examined. It was hoped to interview 955 of the group in 1949 or 1950, in fact, only 592 men attended for examination. The data are presented in great detail, but the prose is tedious and some of the 270 statistical tables are of cursory value. Many of the observations are analyzed as if all these men were suffering from an indistinguishable illness called psychoneurosis; psychiatric diagnosis is descriptive rather than etiologic, and lumping together all psychoneurotics may be as fallacious as drawing conclusions from a study of "heart disease" without further etiologic or pathologic definition. A major goal in this study was to see what happened to these patients after they left the service and to describe their psychiatric status about five years after breakdown. The men's subjective complaints at follow-up are fully recorded, but 41% of these men were receiving compensation at this subsequent examination, and old soldiers do not bite the hand that feeds them. I wanted to find out how many of these men could work in 1950, how well they could work, and what these functions were related to; this information is hard to obtain. The five-year follow-up lacks scientific and objective measurement.

The number of men who are drafted for service varies with military necessity and with the supply of manpower. Standards must be lowered in any all-out military effort, for the manpower pool is not bottomless. To have excluded from World War II all psychiatrically disposed men would have cost about one million men who served without having been admitted to psychiatric care. The neurotics appeared to have paid their way as a group, and the evidence from the book under review favors the employment of the mild neurotic and supports the present military trend away from superficial induction screening and toward more careful fitting of the peg in the appropriately shaped hole. The final 12 pages discussing the implications of this report for induction, employment, and disposition policies are the best of the work and commend it to psychiatrists and all service medical officers, but as a study of the natural history of disease this book is disappointing.

D. B. STONE, M.D.

The Chemistry of Blood Coagulation. By Paul Morawitz, Marburg, Germany; translated by Robert C. Hartmann, M.D., and Paul F. Guenther, M.A., Ph.D., Vanderbilt Unviersity. Price, $4.50. Pp. 194. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

The coagulation of the blood has excited the curiosity of men from Hippocrates and Aristotle to the present. Yet not until the 19th century were the theoretical conceptions of blood clotting founded upon sound experimental facts. This progress came about, as Paul Morawitz suggests in his title, because of a recognition that the blood coagulated as a result of the "fermentative" interaction of "chemical" constituents. In 1832 Johannes Mueller first proved the existence of fibrin in solution in plasma. In 1905 Morawitz assembled the scientific work

of others and himself and formulated a theory of blood coagulation which is still the basis of today's thinking. Thrombin was the catalyst of the fibrinogen-fibrin reaction. Morawitz considered that calcium and thromboplastic substances from platelets, leukocytes, and tissue juice converted the inactive form of thrombin (prothrombin) into the enzymatically active thrombin. A wetable surface was important in this transformation. Once thrombin had formed it was understood that antithrombins rapidly caused its degeneration. Furthermore, fibrinolysis, a second degrading mechanism, was recognized.

Although this book was first published in 1905, its approach is surprisingly modern. Initially one wonders, after surveying the great accomplishments of the 19th century, what remained for the 20th century to develop in the field of blood coagulation. It later becomes apparent that Morawitz and his contemporaries had no knowledge of any plasma thromboplastic factors, such as the antihemophilic and Christmas factors. The roles of vitamin K and its metabolic antagonist, Dicumarol, had yet to be discovered. Heparin was unknown, although its anticoagulant activity following injections of peptone into animals was recognized. Quantitation of thrombic activity and other clotting factors remained for the future to unfold.

Morawitz painstakenly was interwoven the results from 490 experimental contributions to form nine chapters, each a coherent entity. Of special interest is his historical sketch of the theories of blood coagulation before the great conceptions of the 19th century began to emerge. Other chapters deal with calcium, the blood cells, anticoagulants such as hirudin, thrombin, the fibrinogen-fibrin reaction, and tissue clot promoting substances. This is a physiological and chemical study and does not deal with diseases of blood coagulation. The translators, Drs. Hartmann and Guenther from Vanderbilt University, have provided a very readable English text. In addition, confusion in terminology is minimized by their helpful footnotes and by a glossary of terms. This book is the first English translation of Morawitz's important work. It has additional merit because the vast majority of the references dealt with either are inaccessible to the modern student or are written in French and German. "The Chemistry of Blood Coagulation" can be recommended strongly to the consideration of all physicians, physiologists and chemists interested in the clotting of the blood.

W. E. Connor, M.D.

Spondylitis Ankylopoetica (Morbus Strümpell-Marie-Bechterew). By Prof. Dr. Victor R. Ott and Prof. Dr. Hans Wurm. Price, not given. Pp. 246, with 80 illustrations. Dr. Dietrich Steinkopff Verlag, Holzhofallee 35 (16) Darmstadt, 1957.

This 246-page, paper-bound volume is more than a monograph. It can be used as a textbook dealing with this particular type of arthritis, and it is thoroughly and adequately presented by the two authors. It should be in the library of every specialist in the treatment of arthritic diseases and available as a reference book to every physician who treats arthritis in any of its forms. This is the third book of a series which has been planned under the direction of Prof. Dr. Rudolph Schoen, Director of Medicine in the University Clinic and Polyclinic in Göttingen, Germany. The title for the entire series of books, of which this is one volume, is "Der Rheumatismus."

There are 80 beautifully reproduced illustrations, including roentgenograms, photomicrographs, and photographs of completely ankylosed spines which have been prepared by some special technique. Some of these spines were photographed after splitting them saggitally, and these photographic illustrations are remarkable in that a single photographic print appears to have three dimensions, as though viewed through a steriopticon.

The authors have discussed in great detail the techniques of correctly diagnosed spondylitis ankylopoetica, and their reproduction of the x-rays is also remarkable because of the clarity and excellence of detail shown in each x-ray print. A detailed discussion of the theories regarding etiology of this crippling, and often deforming, disease is well presented. The authors describe all methods of treating the disease which are known today. Perhaps the most important section in the book is that which describes the pathology and correlates the x-ray findings with microscopic sections of bone, intervertebral disks, and ligaments of the spine. Again the excellence of these illustrations is deserving of special commendation.

The bibliography fills 11 pages and is the most complete of any that this reviewer has seen. This book has been carefully and accurately prepared, and the material is presented concisely and effectively. It should be translated into English and made available to the large group of physicians and surgeons who find the German language difficult.

Edmard L. Compere, M.D.

Der Lungenboeck im Roentgenbild. By Prof. Dr. Karl Wurm, Prof. Dr. H. Reindell, and Prof. Dr. H. C. L. Heilmeyer. Price, $18.55. Pp. 220, with 214 illustrations. Georg Thieme Verlag, Stuttgart, Germany, Herdweg 63 (14a), Stuttgart N (American Agent—Grune & Stratton, Inc., 381 4th Ave., New York 16), 1958.

The present monograph is based on a study of over 300 cases of sarcoidosis seen by the authors. This unusually large number of cases reported from one institution results from the affiliation of a sanitarium for chronic eye disease with the Department of Medicine at Freiburg University, Germany. The authors report an incidence of bilateral hilar lymphadenopathy in slightly over 6% of 5000 patients with chronic eye disease. During the course of observation in most of these roughly 300 patients the pulmonary findings were interpreted as manifestations of sarcoidosis. In 80 the diagnosis was histologically ascertained. The radiographs of these patients were used exclusively for the illustrations of this atlas.

The illustrated portion of the book is preceded by a short historical review of sarcoidosis. Symptomatology, physical findings, age and sex incidence, tuberculin sensitivity, the Kveim-Nickerson skin test, and other clinical features are discussed. The results of steroid therapy in 65 patients are reported. The influence of pregnancy on the course of the disease is discussed in 12 patients observed by the authors.

On the basis of their own studies on the course of sarcoidosis and the pathology encountered the authors distinguish three stages of pulmonary and mediastinal involvement:

Stage 1. Bilateral hilar lymphadenopathy alone without parenchymal involvement.

Stage 2. Bilateral hilar lymphadenopathy with lymphogenous and/or hematogenous spread to the pulmonary parenchyma. This includes accentuated perihilar markings, diffusely disseminated and solitary miliary and larger infiltrates up to about 9 mm. in diameter.

Stage 3. Conglomerate, large nodular infiltrations and fibrosis of the parenchyma.

The illustrations document the radiographic findings for each stage. Their interrelationship and the course of the disease with its remissions, exacerbations, and arrest of the process are depicted in serial x-rays. In each case the pertinent clinical data are given and the illustrations are explained in detail.

The last part of the book reviews systematically the differential diagnosis of the x-ray findings in sarcoidosis, documented with appropriate case histories and x-rays.

In the foreword the authors state that they have purposely refrained from a discussion of the literature until a later date (to be published in "Handbuch der Tuberkulose"). This explains the few references quoted in the text and the absence of a bibliography. The illustrations are reproductions of x-ray negatives which may be somewhat unfamiliar to the American reader. The contrast and detail of the x-rays are good. Most of the films are PA views of the chest. Enlargement of sections to the original film size and laminograms are frequently used.

In summary, this is a well-done study of the x-ray features of pulmonary sarcoidosis. Some of the statistical data given would carry more weight if in all patients the diagnosis had been substantiated histologically.

HANS U. WESSEL, M.D.

Die Physiologie des Lymphocytenwechsels und seine Beeinflussbarkeit durch Hormone des Hypophysen-Adrenalsystems. By H. G. Hansen, M.D. Price, $4.40. Pp. 164, with 74 illustrations, Georg Thieme Verlag, Herdweg 63 (14a), Stuttgart N (American Agent—Grune & Stratton, Inc., 381 4th Ave., New York 16), 1958.

Dr. Hansen, a pediatrician, has written a readable and well-organized monograph which deals predominantly with his experiments on cats and guinea pigs. These were designed to throw light on the turnover of lymphocytes and the influence of ACTH or cortisone thereupon. A brief excursion into the usefulness of these hormones in the treatment of lymphatic diseases of childhood is presented as what this reviewer feels is an expendable epilogue. Dr. Hansen's main experimental methods were collection of lymph from the thoracic duct, and labelling of lymphocytes with P^{32} or fluorescent dyes. He found that the life span of lymphocytes is not more than one day, and that corticoids effect the production rather than the destruction of lymphocytes. None of his findings are revolutionary, many of them confirm previous observations by others (which are reviewed conscientiously) and all of them are based on sound work. Speculation, for better or worse, is severely curtailed, and the author's critical attitude toward his own findings is plainly evident throughout the book.

N. S. HALMI, M.D.

News and Comment

ANNOUNCEMENTS

Mary Putnam Jacobi Fellowship.—The Women's Medical Association of the City of New York offers the Mary Putnam Jacobi Fellowship to a graduate woman physician, either American or foreign. This Fellowship will start Oct. 1, 1959, and will amount to $2000, $1000 being available Oct. 1, 1959. The recipient of the Fellowship will be expected to make a report to the committee at the end of the fourth month, following which the second $1000 will be awarded, subject to the approval of the committee. The Fellowship is given for medical research, clinical investigation, or postgraduate study in a special field of medicine. The recipient is expected to devote full time to the Fellowship, but exception may be made by the committee under special circumstances.

Applications for this Fellowship may be obtained from the secretary of the committee, Dr. Ada Chree Reid, 118 Riverside Dr., New York 24, after Aug. 1, 1958, and must be returned before Feb. 1, 1959, with the following information: (1) curriculum vitae, (2) a statement from a physician of a recent physical examination, (3) transcripts of her college and medical school records, (4) personal letters of recommendation from two or more physicians under whom she has studied, (5) a statement by the applicant of the problems she proposes to investigate or the study she plans to undertake, (6) a statement from the person under whom she proposes to study of her interest in her subject, (7) recent photograph. All the above data must be at hand before the application will be considered.

Successful candidates will be notified not later than May 1, 1959.

Course in Interpretation of Complex Arrhythmias.—A course in interpretation of complex arrhythmias will be given at Michael Reese Hospital by Drs. Louis N. Katz, Richard Langendorf, and Alfred Pick. This is an *advanced* course, intended only for experienced electrocardiographers. The class will meet daily from 9:00 a. m. to 5:00 p. m., Dec. 8-12, 1958.

Further information and a copy of the lecture schedule may be obtained from the Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16.

Meeting of American Psychosomatic Society.—The American Psychosomatic Society will hold its 16th annual meeting at Chalfonte-Haddon Hall, in Atlantic City, N. J., on Saturday and Sunday, May 2 and 3, 1959.

The program committee would like to receive titles and abstracts of papers for consideration for the program no later than Dec. 1, 1958. The time allotted for presentation of each paper will be 20 minutes.

Abstracts, in octuplicate, should be submitted for the consideration of the program committee to the Chairman, at 265 Nassau Rd., Roosevelt, N. Y.

Second Oklahoma Colloquy on Advances in Medicine.—On Nov. 12, 13, 14, and 15, 1958, will be held the Second Oklahoma Colloquy on Advances in Medicine, which will be devoted to arthritis and related disorders.

The program has been developed by the Department of Medicine and the Division of Postgraduate Medical Education of The University of Oklahoma Medical Center and is being sponsored by Geigy Pharmaceuticals, Wyeth Laboratories, the Upjohn Company, Pfizer Laboratories, Schering Corporation, and the Oklahoma Chapter, Arthritis and Rheumatism Foundation.

Eleven nationally prominent investigators will participate and present the results of original work and clinical experience.

Registration will be open to all physicians. There will be a registration fee of $25. Members of the Armed Forces, interns, and residents may attend without charge. Interns and residents must present a letter from the chief of staff of their hospital. Further information may be obtained by writing the Office of Postgraduate Education, The University of Oklahoma School of Medicine, 801 Northeast 13th St., Oklahoma City.

Football fans everywhere will be interested in the Missouri-Oklahoma game held at Norman, Okla., on Nov. 15, the final day of the meeting. Norman is some 20 miles from the Medical Center, where the program is being held.

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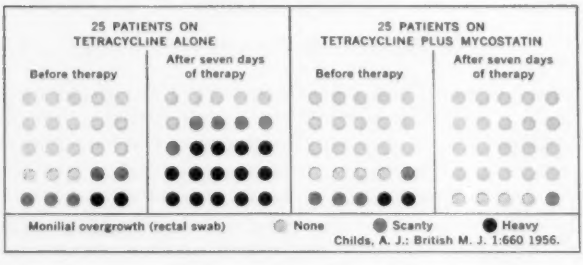

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2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:504, *Dec. 1957.*

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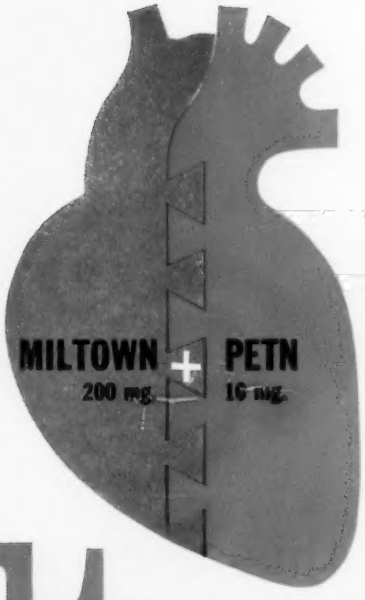

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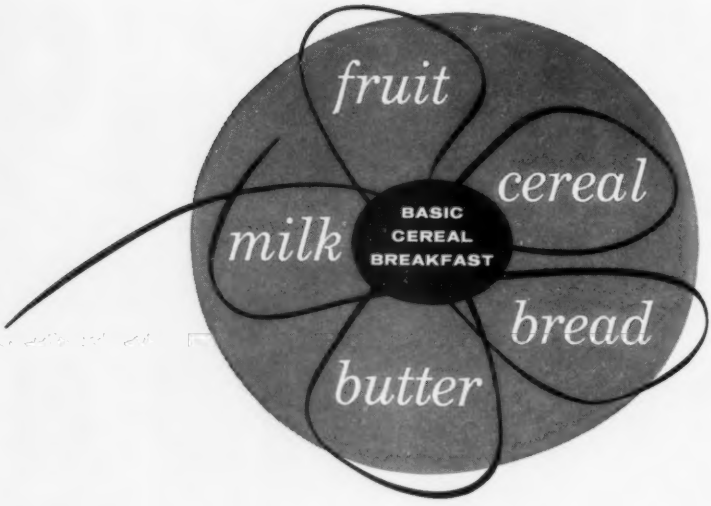

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Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used. 8th ed. Philadelphia: A. deP. Bowes, 1956.
Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
Hayes, O. B., and Rose, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.
Cereal Institute, Inc.: A Summary of the Iowa Breakfast Studies. Chicago: Cereal Institute, Inc., 1957.

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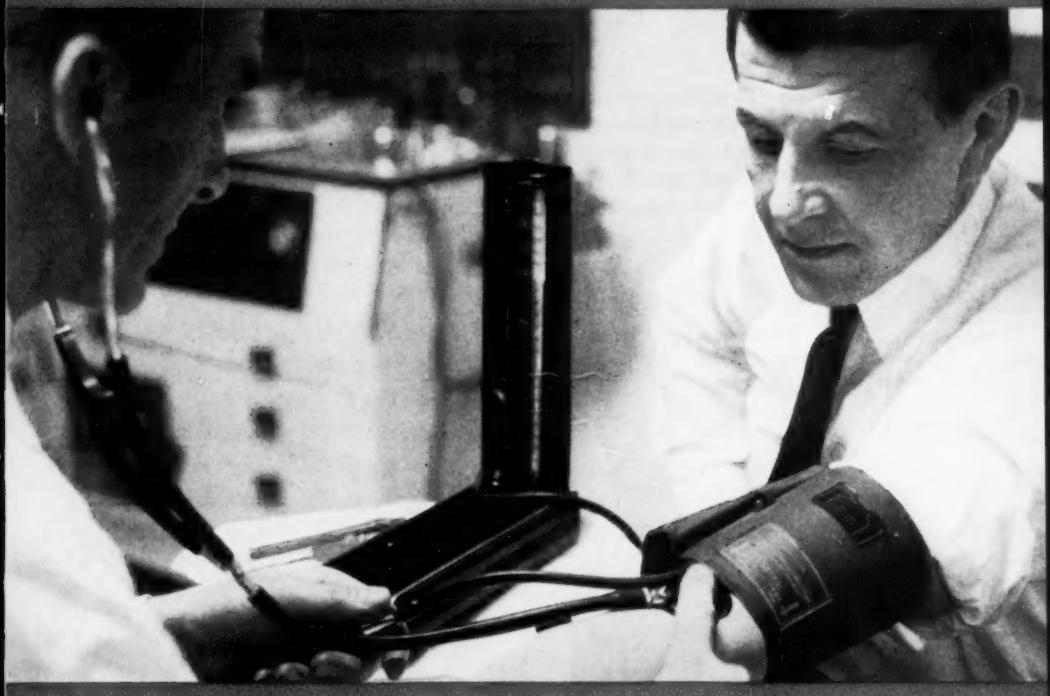

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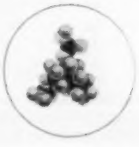

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Jordan and Grossman; Arch. Surg. 74: 871, 1957
Shingleton, et al; Surgery, 42: 12, 1957
Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956
Krane; Am. Pract. and Digest, 8: 1275, 1957

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COMPAZINE* SPANSULE†

AN OUTSTANDING TRANQUILIZER IN SUSTAINED RELEASE DOSAGE FORM • Also available:

Tablets, Ampuls, Multiple dose vials, Suppositories and Syrup.

Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F. †T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.